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Journal of The Royal Australasian College of Physicians

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AUSTRALASIAN ANNALS OF MEDICINE

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MICRODISSECTION STUDY OF NEPHRONS AND CYSTS FROM AN INFANT WITH PYELONEPHRITIS[1]

DORA BIALESTOCK[2]

SUMMARY

A unilateral non-functioning kidney removed from a premature neonate because of pyelonephritis was examined by microdissection. This showed a degree of change which was not apparent on simple histological examination.

Microdissection of the kidney showed it to be composed predominantly of nephrons which had short poorly-convoluted proximal tubules with only rudimentary loops of Henle. Along the length of the normal structures localized dilatations were not infrequently found. Gross cystic changes were demonstrated in glomeruli, tubules and collecting ducts, and measurements of some of the normal and grossly abnormal structures are recorded.

THE stability and constancy of form of body tissues has always given rise to the view of their rigid immutability; this is widespread and influences many of the opinions on the mode of development of pathological processes. Careful study, over the last few decades, has revolutionized this concept, and it is now realized that living tissues are in a state of dynamic equilibrium—processes of growth and degeneration are continually active.

The processes responsible for normal growth begin at the inception of embryonic life, and, though they become slower and at times imperceptible, they continue for as long as the tissue is viable. The formation of nephrons which occurs during embryonic life is practically complete at term, and the kidney of the full-term infant does not grow appreciably in the number of nephrons, but, from then on, for some time there is increase in the length and complexity of the existing functional units (Potter, 1952).

At any stage the normal stimuli may be altered or interrupted, and thus aberrant forms of growth follow. These may be in the direction of increased or diminished growth, and, in the second case, inhibition may be followed (in due course) by renewed normal or increased activity. These permutations and combinations of different types and degrees of change result in complex patterns of structure which require close study for their elucidation.

In the material to be discussed the abnormal growth patterns are seen in the gross cystic changes to be described. These changes were found scattered at random along the length of the nephrons: in glomeruli, convoluted tubules and collecting tubules (Figures VI, VII, VIII, XII, XIII and XVIII). This distribution was a feature of the material studied, and only by a method by which the nephron can be seen in its full length could the diverse distribution and changes be followed with any certainty. Such a method was provided by the technique of microdissection.

CLINICAL HISTORY

A male baby, born prematurely of healthy parents, had a birth weight of six pounds two ounces. The pregnancy had been uneventful until the thirty-sixth week, when the mother developed severe diarrhoea, which lasted intermittently for ten days. This illness was followed rapidly by the onset of premature labour. Actual labour was uneventful.

When the baby was three days old he was pale and listless, refused to suck, passed a number of loose motions containing mucus and was found on investigation to have a Shigella dysentery which responded slowly to chemotherapy.

At the age of three weeks the infant had not thrived. Microscopic examination of urine showed copious pus cells.

[1] Received on October 28, 1957.

[2] Georgina Sweet Fellow in Medicine, Department of Pathology, University of Melbourne.

Intramuscular pyelography showed an almost completely non-functioning left kidney, but the right kidney functioned normally. Left nephrectomy was performed when the infant was five weeks old.

Convalescence was uneventful, and since operation nine months ago the infant has made satisfactory progress. A micturating cysto-urethrogram prepared at the age of three months demonstrated reflux into the remaining renal pelvis.

FIGURE I

Macroscopic view of the intact kidney (above) with a normal kidney from a baby of the same age (below). Small white areas of abscess formation may be seen in the upper kidney, especially at its left-hand side

PATHOLOGICAL STUDY OF LEFT KIDNEY REMOVED AT OPERATION

Macroscopic Examination

The kidney was smaller and paler than a normal organ from an infant of the same age (Figures I and II).

The capsule stripped easily, and round white patches could be seen with ease diffusely scattered throughout the organ. On hemisection the cortex was seen to be narrowed; there was blurring of the cortico-medullary junction. The white patches, which were multiple abscesses, extended throughout the renal parenchyma from the subcapsular cortex to the medulla adjacent to the dilated, thickened, hydronephrotic pelvis (Figure II). The pelvic epithelium was smooth, and no direct communication was observed between the pelvis and the abscesses. No information on the condition of the ureter was obtainable.

Microscopic Study

A narrow nephrogenic zone of developing renal tissue was still visible immediately beneath the capsule (Figure III). The cortex was narrower than normal, and many scattered abscesses containing lymphocytes, plasma cells, macrophages and relatively few polymorphs were seen throughout the renal parenchyma.

FIGURE II

The abnormal and normal kidney in hemisection (cf. Figure I). Note the narrowed cortex, the blurred cortico-medullary junction and the abscesses, especially at the left-hand side. The smooth epithelium of the hydronephrotic pelvis is apparent

Glomeruli presented a variable appearance: some possessed normal tufts containing a few red corpuscles and a normal capsular space; others were shrunken and atrophic, and in a few the capsular space was mildly dilated. True cysts could not be identified in the sections

examined. A number of glomeruli showed cellular crescents and the onion-skin thickening of the capsule—described by Porter and Giles (1956) as being typical of the pyelonephritis of the newborn. Tubules were well formed, and the lining cells were not atrophic. A mild degree of dilatation was present in the collecting tubules (Figure IV). Amorphous eosinophilic deposits and granular basophilic nuclear debris could be identified in the lumina of some tubules. An inflammatory cell infiltration was present in the interstitial tissues. Small and medium-sized arterioles showed thickening of their walls.

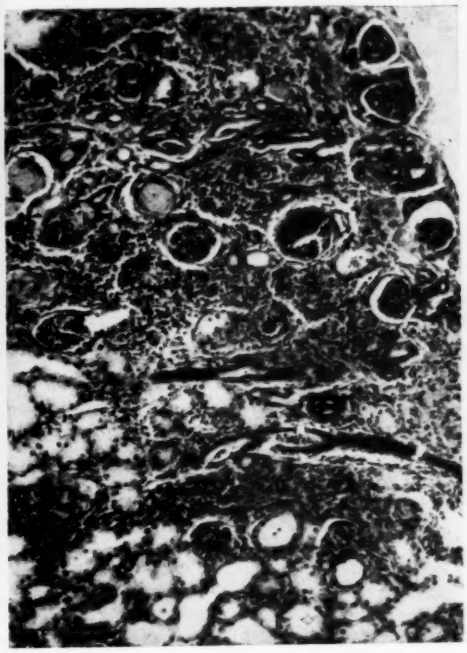

FIGURE III

Photomicrograph of a section of a subcapsular cortex. The nephrogenic zone is visible at the upper right-hand corner. There is profuse cellular infiltration of the interstitial tissue. Degenerate glomeruli are present in varying stages of change. ×90

MICRODISSECTION

Method

The method of Oliver *et alii* (1951) was followed. Formalin-fixed tissue was cut into small wedges from capsule to pelvis. These fragments were placed in concentrated hydrochloric acid for about 72 hours. When the tissue was considered to be soft enough for dissection, small fragments of the macerated tissue were placed on the stage of a stereoscopic dissecting microscope and manipulated with needles. Measurements of the nephrons and other components were made by means of an eyepiece graticule calibrated against a standard

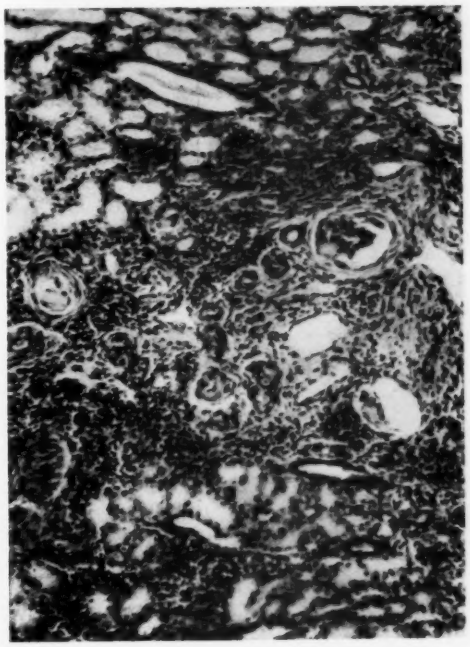

FIGURE IV

Photomicrograph of a section from deeper in the cortex. The crescentic and onion-skin capsular thickening of the capsule is well shown. There are inflammatory cell infiltrations, and at the upper left-hand corner there are a few dilated collecting tubules. ×90

millimetre. Photographs were taken using Pan F film with a 35-millimetre camera attached to one of the eyepieces.

Microdissection Findings

As soon as dissection was begun, abnormal large cysts were seen with ease.

The "normal" nephron was, however, numerically the most prominent constituent, outnumbering abnormal structures by about twenty to one (Figures V and IX). "Normal" glomeruli were round or slightly ovoid in shape, and the average diameter of 20 that were measured was 90μ. However, considerable variation was evident in glomerular dimensions, as the measurements for the following six consecutive diameters recorded were 60μ, 75μ, 60μ, 60μ, 90μ and 90μ.

FIGURE V

Photomicrograph of a microdissected glomerulus and proximal convoluted tubule showing the flabby, poorly-convoluted tubule. ×96

FIGURE VI

The large cyst at the upper right-hand corner is still attached to a tubular stump. At the lower left-hand corner a normal glomerulus is attached by a thin attenuated neck to the proximal convolution. ×96

FIGURE VII

Photomicrograph of a segment of a normal infantile proximal convolution, showing the area of localized dilatation commonly seen along the length of the nephrons. ×96

FIGURE VIII

A cyst of bizarre shape, possibly formed partly from glomerulus and tubule; it is still attached to a straight collecting tubule. ×96

FIGURE IX

Entire glomerulus and proximal tubule demonstrating the normal neck segment, with a localized dilated region just below the neck. The rudimentary loop of Henle is seen at the lower pole of the illustration

FIGURE X

Photomicrograph of a large irregular cyst attached by a short flabby tubule to what appears to be an almost normal glomerulus. ×96

FIGURE XI

A bizarre-shaped cyst attached to a narrow straight tubule. ×96

FIGURE XII

Photomicrograph of dissected tissue from high up in the almost normal collecting tubules. Note that the left-hand side of the Y-shaped segment shows a localized dilatation. ×96

FIGURE XIII
A large glomerular cyst attached to a flabby poorly-convoluted but otherwise normal infantile tubule. ×96

FIGURE XIV
An isolated medium-sized glomerular cyst with a normal glomerulus below it for comparison. ×96

FIGURE XV
Photomicrograph of a large irregular cyst. The cellular wall was quite tough and well formed. ×48

FIGURE XVI
Small isolated cyst of irregular shape. This had no apparent connexion with any tubule. ×96

Proximal tubules, dissected with their glomeruli, were 20μ to 30μ in diameter, and lengths of one to three millimetres were recorded in the six examples measured. Precise measurements were not easy to obtain in all cases, as some of the tubules were not available in their complete length.

FIGURE XVII

Photomicrograph showing five specimens of glomerulus and the neck segment of the proximal convoluted tubule demonstrating the diversity of appearance found in this region. ×96

The neck and first part of the proximal tubule were observed with special interest following Darmady and Stranack's (1957) microdissection reports on the significance of changes in this region in other material from infants and children.

The neck showed perhaps more variation than other parts of the tubule, varying in appearance from just a short constriction joining the glomerulus to the proximal tubule, a piece of tubule is no way distinguishable from the flabby dilated poorly convoluted infantile proximal tubule, a localized dilatation in a narrower tubule, or the long thin attentuated segment described by Darmady and Stranack. When the neck was thin and attenuated, the attached glomerulus was often small and atrophic (Figure XVII).

FIGURE XVIII

Photomicrograph showing large grossly dilated collecting tubules; the normal distal tubules are entering the left-hand arm. ×48

Two distal tubules were measured; both were 20μ in diameter, and they were 1·2 and 1·8 millimetres long respectively.

Very few Henle's loops were seen, and the thin segment was often only rudimentary (Figure IX). The thick segments could be distinguished only by their lack of convolution. Only one straight thick segment was measured, and this was 20μ in diameter and 0·9 millimetre long. Three nephrons with what appeared to be almost complete proximal convoluted tubules were measured; the measurements were as follows:

1. Glomerulus: 60μ diameter. Proximal tubule: 30μ diameter, 1·8 millimetres long.

2. Glomerulus: 90μ diameter. Proximal tubule: 30μ diameter, 1·8 millimetres long.

3. Glomerulus: 75μ diameter. Proximal tubule: 30μ diameter, reaching 60μ in a dilated segment, 3·0 millimetres long.

FIGURE XIX

The upper end of a dilated collecting tubule showing the blind clubbed termination seen in some of these. ×48

One normal collecting tubule was measured; it had a diameter of 30μ and was 0·72 millimetre long.

Nephrons which were regarded as "normal" fell within a relatively wide range and showed considerable variability, because dilatations along the length of a tubule were not unusual (Figures VII, IX and XII). The frankly abnormal structures were the cystic dilatations. Some glomeruli were only slightly larger than the normal, but others showed gross enlargement yet still retained their round glomerular shape, so that their origin was in no doubt (Figures VI, XIII and XIV). Tubular aberrations were again variable, ranging from small localized dilatations only in tubules of otherwise normal calibre (Figures VII and XII) to large bizarre structures whose origin was probably tubular, but not demonstrably so (Figures VIII, X, XI, XV and XVI). Some of the cysts were measured and the following observations were made: round glomerular cyst, 195μ×180μ; ovoid cyst, probably glomerular, 180μ×240μ; large, probably tubular, cyst, 300μ×720μ.

Most of the collecting tubules showed gross enlargement due to distension of the lumen. One of these tubules was 120μ in diameter and 0·9 millimetre long.

The measurements of a group of distended tubules, with one large cyst attached to the collecting ducts by a straight tubule, were recorded. The cyst was 300μ in diameter, and the tubule connecting it to the collecting tubule was 60μ in diameter and 0·72 millimetre long.

The dilated ducts into which the tubule opened were Y-shaped. One arm was 75μ in diameter and 0·9 millimetre long; the other arm was 90μ in diameter and 1·3 millimetres long. The lower part into which both of these drained was 150μ in diameter and 0·36 millimetre long. When the dilated lower part of collecting tubules were dissected to their origins within the renal substance, a few were found to end as blind clubs without any obvious connexion with the proximal part of collecting tubules (Figure XIX). However, even when the upper end terminated blindly, collecting tubules often entered lower down the length of the dilated tubule (Figure XVIII).

COMMENT

The measurements recorded, although of some interest, cannot have much value without the existence of normal data for comparison. Oliver (1956) said: "I am fairly certain that in mammals no one has more than a vague guess even to the size or diameter of any physical measurement of even the proximal convolution, much less the remainder of the nephron."

The need for accurate baselines of renal structures to allow correlation with hypotheses of the function of various parts of the nephron is of particular importance in the infant, where so many problems of clinical management are intimately bound up with an accurate assessment of the way the newborn animal establishes homœostatic equilibrium. Such study is being undertaken. The kidney remains the most important structure in the maintenance of the constant internal environment necessary for the independent existence of the young animal. The presence of cystic changes in this case brings to mind the theoretical notions of their

formation. Current hypotheses were discussed in a recent paper (Bialestock, 1956). The findings in this case are in the main similar to those previously described: the cystic changes are diverse in appearance and may occur anywhere along the length of the nephron; they may involve glomeruli, tubules and collecting ducts. The hypothesis which is currently regarded as best fitted to explain these observations is that of Moolten (1943), quoted by Gruenwald (1947). The distribution and variability of the changes strongly suggest a disturbance in organizer action during development, such development not being necessarily final at birth. The presence in this material of clubbed blind ends in the collecting tubules would suggest that the simple mechanical theory of non-union of separately developed embryonic components (von Mutach, 1895) may play a part. This, of course, is merely a facet (viewed from the morphological point of view) of the previous concept.

Virchow's suggestion (1869) that scarring following either crystal deposition or infection might cause cyst formation in infants, though superficially applicable in this case, does not survive close scrutiny. When one considers the large well-formed cysts which have been the site of cellular hypertrophy and hyperplasia, yet in which there is no relation whatever with the surrounding inflammatory changes, it is apparent that processes other than simple obstruction must be invoked. One is inclined to the opinion that infection became localized in an organ already abnormal, rather than that the abnormality followed the inflammation.

Whether this type of case bears any relation to the adult form of polycystic disease or whether cysts will continue to grow at the expense of normal nephrons is open to conjecture.

The important observation in this case is the occurrence of cysts of various degrees and types of development at different sites in the nephrons. This suggests that the processes were active over a considerable period, affecting different parts at different times. The degree of disturbance has been relatively mild, as shown by the relatively small number of nephrons affected and also by the normal condition of epithelium even when it is part of structures which are themselves atypical (that is, cysts).

The precise nature of the stimuli producing these effects is not known, but the changes are mediated by the various "organizer" stimuli, both physical and chemical, determined by adjacent tissues as well, presumably, as more distant agents. The observations of the morphological features are a necessary precursor to the more complete understanding of these conditions. Many of these observations can be made only by a method which shows the relation of the various parts of the nephron and those parts *in toto*, as in the technique of microdissection discussed here.

ACKNOWLEDGEMENTS

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THE LIMITING TEMPERATURE FOR THE TRANSMISSION OF DENGUE[1]

E. H. DERRICK[2] and VALERIE A. BICKS[3]
From the Queensland Institute of Medical Research

SUMMARY

As *Aëdes ægypti* is susceptible to dryness as well as to cold, the wet-bulb scale is more suitable than the dry-bulb to define the temperature associations of a dengue epidemic.

Epidemics of dengue in Brisbane in 1942 and 1943 ceased when, at the approach of winter, the mean wet-bulb temperature fell to about 14° to 15° C (57° to 59° F).

The line in New South Wales where the 1926 invasion of dengue halted can be represented approximately, but not exactly, by the mean annual wet-bulb isotherm of 14·2° C.

A coastal strip across the north of Australia meets the temperature requirements for the endemicity of dengue. However, the paucity of sufficient concentrations of population in this strip and the explosive character of Australian outbreaks make the existence of any endemic foci in Australia very unlikely.

DENGUE, which is endemic in certain tropical areas, makes periodic invasions into the subtropics. The extent and duration of these invasions are determined, by, *inter alia*, the temperature gradient. Observations made on two invasions along the east coast of Australia allow an estimate to be made of the temperature at which transmission ceases.

The fall of temperature which terminates an outbreak may be due to the approach of winter or to increase in latitude or altitude. It can act in two ways—by reduction of the number of biting *Aëdes ægypti* and by reduction of their infectivity.

The sensitivity of *A. ægypti* to cold, reported by many authors, may be exemplified by the observations of Lewis (1933). In a laboratory colony in London, he found that biting activity was greatest between 25° and 30° C.; at 15° general activity was much reduced, hardly any mosquitoes flying and none biting; at 10° they became dormant. In recent years, Brisbane has been free from *A. ægypti*, but when it was a pest, as in 1942 and 1943, adults virtually disappeared in winter, although search might disclose larvæ. The normal[4] mean temperature in July, the coldest month, is 15° dry-bulb, 11·8° wet-bulb.

Blanc and Caminopetros (1930), working in Athens, reported the suppression by cold of the infectivity of mosquitoes previously infected with dengue virus. While the temperature of the mosquito room was about 20° to 22°, the mosquitoes transmitted the disease to experimental subjects on which they fed, but failed to do so when, in the winter, the temperature of the room fell to an average of 16·4°. From their Figure VI, the borderline was about 18·5°. However, the mosquitoes remained active at the winter temperature, biting, engorging and breeding. That is, with falling temperature, infectivity was lost before biting activity.

Humidity must also be taken into account. Blanc and Caminopetros noted considerable mortality in their mosquito colony if the humidity was insufficient, and Lewis found that biting activity was reduced and the life of unfed specimens shortened by low humidity. It seems likely, therefore, that the wet-bulb scale, which gives a combined measure of temperature and humidity, is more suitable than the dry-bulb scale to define the temperature associations of a dengue outbreak, and this conclusion is supported by the present study.

THE LIMITING TEMPERATURE IN BRISBANE IN 1942 AND 1943

After an absence of about 16 years, dengue arrived in Brisbane from the north early in 1942, and appeared again in 1943. As it is not notifiable, there is no record of the total incidence, but the cases admitted to the Brisbane Hospital, although a very small fraction of the whole, indicate the course of the epidemics. These began in summer, had their peaks in autumn and ceased in or just before winter. From February 5 to July 9, 1942, admissions numbered 116, and from January 23 to June 2,

[1] Received on October 16, 1957. Read in part at the Ninth Pacific Science Congress at Bangkok beginning November 18, 1957.

[2] Deputy Director.

[3] Assistant Research Officer.

[4] In this paper, "normal" as applied to weather records means the average over 30 years.

1943, they numbered 87. There are gross figures and include doubtful cases and some with post-dengue manifestations.

The mean temperature for February, 1942, was 23·7° dry-bulb and 20·4° wet-bulb, and for January, 1943, it was 24·8° and 21·2° respectively. During subsequent months, the temperature progressively fell, except that in 1942 it was higher in March than in February. It is during the closing stage of the epidemics that the temperature is most informative. Table I and Figure I show weather data for Brisbane in relation to the last cases.

TABLE I

Weekly Records of Temperature, Humidity and Rainfall in Brisbane, Before and After Ending of Dengue Epidemics[1]

Week Ending :	Mean Dry-Bulb Temperature (°C.)		Mean Wet-Bulb Temperature (°C.)		Mean Relative Humidity (%)		Rainfall (Points)	
1942 :								
May 21 ..	18·3		14·4		63		0	
May 28 ..	19·2		16·2		72		111	
June 4 ..	15·9	17·9	11·2	14·6	53	68	0	36
June 11 ..	17·3		14·5		72		47	
June 18 ..	18·9		16·7		79		44	
June 25 ..	17·6		14·3		68		12	
End of Epidemic								
July 2 ..	17·3		13·2		60		14	
July 9 ..	17·1	16·8	13·8	13·2	67	64	39	42
July 16 ..	17·1		14·1		70		65	
July 23 ..	15·8		11·9		61		48	
1943 :								
April 26 ..	19·6		13·7		48		27	
May 3 ..	19·9	19·7	16·4	15·3	67	60	10	25
May 10 ..	19·7		15·1		58		0	
May 17 ..	19·7		16·1		67		62	
End of Epidemic								
May 24 ..	18·7		14·2		59		6	
May 31 ..	16·6	16·7	13·2	13·1	65	64	3	32
June 7 ..	15·4		11·7		62		102	
June 14 ..	16·0		13·2		70		19	

[1] The daily maximum dry-bulb temperature averaged about 5° more, and the minimum about 5° less than the means shown; the wet-bulb about 3° more or less.

Cases in which, on review of the record, the diagnosis of dengue seemed questionable have been excluded, as well as cases apparently infected outside Brisbane. The onset of the last acceptable case in 1942 was on July 2, and in 1943 on May 24. For each case a presumptive date of infection seven days prior to the date of onset has been adopted, to allow for the incubation period, which may vary from four to fifteen days, and averages six or seven days.

During the closing stages of the 1942 epidemic, the mean daily temperature showed large wave-like fluctuations, which are still evident in Figure I, although the curve has been smoothed by plotting weekly means. Over the last six weeks, the mean dry-bulb temperature was 17·9°, and the mean wet-bulb temperature 14·6°. These figures may be compared with those for the four weeks after cases ceased, when the means were 16·8° and 13·2° respectively. It may be noted that the weather had been colder than this for a short time without ending the epidemic. For six consecutive days up to June 3, the mean daily temperature remained at about 15·5° dry-bulb and 10·8° wet-bulb, but infection continued for another three weeks. However, the epidemic did end several weeks before the weekly means again approached these levels towards the end of July.

The winter of 1943 was colder than that of 1942, and the dengue epidemic ended more than five weeks earlier. During its last four weeks, the temperature was comparatively steady, the means being 19·7° dry-bulb and 15·3° wet-bulb.

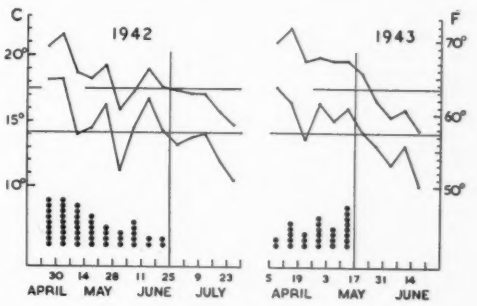

FIGURE I

Mean weekly temperature in Brisbane, before and after ending of dengue epidemics in 1942 and 1943. Upper curves represent the dry-bulb readings, lower curves the wet-bulb. Spots represent cases, grouped in weeks, at the presumptive time of infection

From about the time of the last case, the temperature fell rapidly, and the means of the four post-epidemic weeks were 16·7° dry-bulb and 13·1° wet-bulb.

The lines on the graph which seem to divide best the epidemic weeks in 1942 from those following lie at about 17·5° dry-bulb and 14·2° wet-bulb. The more abrupt fall of temperature in 1943 gives a wider range of selection. Taking both years into account, the limiting temperature might be estimated at 17° to 18° dry-bulb and 14° to 15° wet-bulb. Approximate Fahrenheit equivalents are 63° to 64° and 57° to 59° respectively.

It may not be assumed that the Brisbane temperatures quoted above were the same as those surrounding the biting mosquitoes. Whereas the official Brisbane temperatures are taken outdoors in a louvred screen of standard type, it is the custom of *A. ægypti* to shelter indoors, where the environment would be

warmer. In this connexion, Mr. B. W. Newman, Bureau of Meteorology, Brisbane, has given me the following note.

> The mean dry-bulb temperature inside our main office seems to be of the order of 2° C warmer in summer and 3° warmer in winter than the outside screen temperature. In the dark corners of a residence where the mosquitoes hide, the temperature would have less diurnal range than in an office, but the actual mean temperature may be of the same order.

The Brisbane estimate of the limiting dry-bulb temperature is, in fact, slightly lower than that observed in the laboratory of Blanc and Caminopetros. The sheltering custom could explain also the persistence of the epidemic through the short spell of weather in 1942 which was colder than that prevailing when it ended.

Relative humidity and rainfall for the relevant periods are also noted in Table I. These varied from week to week, but no striking changes were associated with the cessation of cases. To what extent the anti-mosquito measures provoked by the epidemics contributed to their control is not clear. It was certainly not a lack of susceptible subjects that ended the 1942 epidemic, for cases recurred in 1943.

Whatever factors, other than temperature, may have contributed to the ending of the epidemics, it remains that a temperature adequate for the transmission of dengue virus from mosquito to man prevailed in Brisbane up to June 25, 1942, and May 17, 1943.

The Temperature Limiting Geographical Extension in New South Wales in 1926

When dengue invaded New South Wales in 1925–1926, the line where it halted was carefully recorded by Ferguson (1928). This curved from Bourke and Walgett to the Newcastle district (Figure II). The most southerly point reached was Gosford (33·4° F). Sydney remained free. Spread was limited also by altitude; Inverell (1980 feet) and Tenterfield (2831 feet) were invaded, but not places on the New England tableland over 3000 feet.

The two flanks of the line of invasion, Bourke and Newcastle, differ considerably in climate. Bourke, 400 miles inland and 361 feet in altitude, is comparatively dry and with a greater range of temperature; the normal mean dry-bulb temperature is 28·7° in January and 11·3° in July. Newcastle, on the coast, is more humid and more equable; corresponding figures for January and July are 22·3° and 12·6°. It seems unlikely that the limiting line can be represented by any dry-bulb isotherm. That for an annual mean of 17·8°, selected because it separates Newcastle and Sydney, would exclude much invaded territory in Queensland, as well as some in New South Wales, and include much that was uninvaded in western New South Wales (Figure II).

A much better approximation to the line is given by the annual wet-bulb isotherm of 14·2°. This, however, is not a perfect fit, for it excludes Killarney (where a brisk outbreak of dengue was observed by the writer in the last week of March, 1926) and Inverell, and includes Sydney as well as Wollongong, further south.

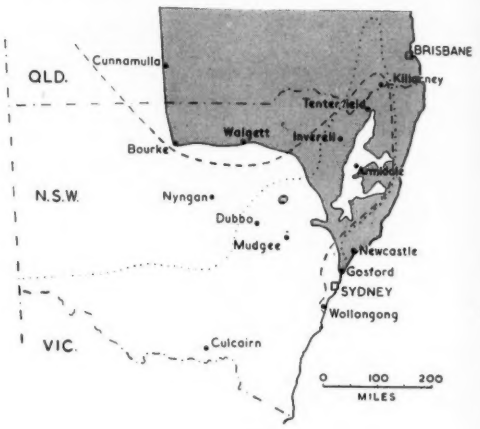

FIGURE II

Map showing the southern extension of dengue in 1926. The invaded area is shaded. The distribution in New South Wales is taken from Ferguson (1928). He accepted the contour line at 3000 feet (shown surrounding Armidale) as the limit of extension altitudinally. Records of the distribution in Queensland are scanty, but probably most towns from Cunnamulla to Brisbane were invaded. Dotted line: 17·8° dry-bulb annual isotherm. Broken line: 14·2° wet-bulb annual isotherm

Figure III shows that the use of the wet-bulb scale brings the mean monthly temperature curves for the invaded places close together, particularly in the warmer months, which are the significant ones for dengue transmission. For instance, the wet-bulb difference between Bourke and Newcastle for January, 1926, was only 0·6°, in contrast to the dry-bulb difference of 4·6°. (Normally the wet-bulb temperature is 19·3° at both Bourke and Newcastle in January, whereas, as noted above, the dry-bulb differs by 6·4°.) The curves for Killarney and Walgett, omitted to avoid confusion, were close to that for Bourke, usually above it. It will be be noted that the curve for Sydney, the warmest of five uninvaded places studied, was always

above that for invaded Inverell. The temperature in Sydney, therefore, appears adequate for dengue; as noted later, its freedom may be explained by the absence of *A. ægypti*.

The temperature prevailing at the time of outbreaks in three towns may be studied in Figure III. Their full duration was not always recorded, but the following dates when cases occurred were given by Ferguson: Bourke, February 1 (first indigenous case) to May 5; Inverell, February 7 (first case) to March 4 (epidemic abating, but not over); Newcastle, end of November to April. As far as may be judged from monthly means, the wet-bulb temperature would have exceeded 14·2° on the dates of infection, except perhaps for the case at Bourke with onset on May 5. These observations are in general accord with the conclusion derived from the Brisbane epidemics.

In 1926, the February temperature was unusually high throughout northern New South Wales—a fact reflected by the peaks in the curves in Figure III. It was in February that the outbreaks in Bourke and Inverell were at their height and a sharp increase of cases occurred in Newcastle.

Perfect correlation of temperature with the activity of dengue is, of course, not to be expected, for other factors are influential. The presence of absence of *A. ægypti* is all-important.

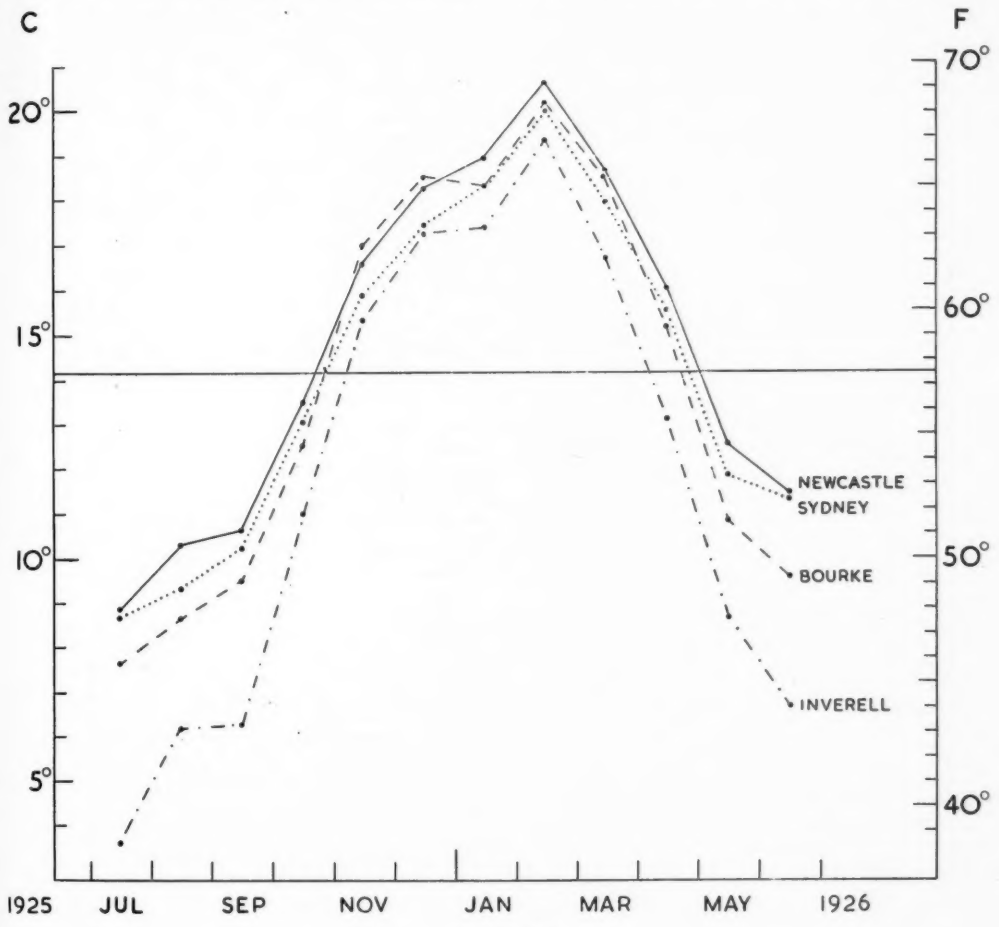

FIGURE III

Mean monthly wet-bulb temperature at three invaded localities and at Sydney from July, 1925, to June, 1926

There is evidence that this introduced mosquito has progressively extended into New South Wales from the north. Ferguson considered that, in 1926, its distribution corresponded closely with that of dengue. He noted, however, that his survey was incomplete. In 1923, he had reported that collecting in New South Wales had failed to show that it occurred much further south than Newcastle; certainly it was absent from the Sydney and Hawkesbury River districts. Since then (O'Gower, 1956), *A. ægypti* has been found in many inland places beyond the dengue line as far south as Culcairn (35·7° S). This may represent, at least in part, a later extension.

In Figure IV, the wet-bulb isotherm for 14·2° has been extended across Australia. One should be cautious in drawing conclusions from its course in the drier interior, but it appears that a suitable temperature for the spread of dengue is found in Western Australia much further south than Carnarvon (24·9° S), the most southerly locality from which it has been reported (Lumley and Taylor, 1943). O'Gower notes that *A. ægypti* has been collected as far south as Harvey (33·1° S), 78 miles south of Perth.

FIGURE IV

Dengue zones. The upper curve on the map of Australia is the 14·2° wet-bulb isotherm for July, approximately north of which the temperature is suitable for the persistence of dengue throughout the year. The lower curve is the annual 14·2° wet-bulb isotherm, which may indicate approximately the southern limit of dengue invasions

LIMITING TEMPERATURE AND ENDEMICITY

If dengue can be transmitted when the mean wet-bulb temperature is at least 14° or 15°, transmission might be continuous throughout the year, as far as temperature is concerned, in places where the winter temperature does not fall below this level. In Australia, the 14·2° wet-bulb isotherm for July delimits a coastal strip across the top of the continent from Cossack (20·7° S) in Western Australia to Mackay (21·15° S) in Queensland (Figure IV).

How does theory fit the facts?

In North Queensland, it is unlikely that dengue has persisted endemically through the intervals between epidemics. The length of the intervals (up to fifteen years), the explosive nature of epidemics, and the high proportion of population affected[1] argue strongly against endemicity. Reports of occasional interepidemic dengue-like cases may readily be explained by the uncertainty of clinical diagnosis of sporadic cases. Some were probably cases of leptospirosis, for this disease is now known to have a high frequency and a wide distribution in North Queensland, the duration of fever is similar, and mild forms do not show the distinctive feature of jaundice. Leptospirosis would fit well, for instance, the cases reported by O'Brien (1908) in Cairns "resembling dengue in every detail except for the absence of rash and the third-day remission". In Malaya, Fletcher (1928), after recognizing the presence of leptospirosis, reported his belief that it had hitherto been confused with dengue.

In Darwin, dengue is reputed to have been endemic and occasionally epidemic prior to World War II (Kirkland, 1939; Lumley and Taylor, 1943; Miles and Dane, 1956). This is no reason to question the nature of the epidemics, but, as reports are few and with little detail, the published evidence is insufficient to prove endemicity. Leptospirosis, which had not been recognized in the Northern Territory when Kirkland reviewed its diseases, is now known to be present there in a variety of types (Wannan, 1955). After the abolition of domestic water tanks, *A. ægypti* could no longer be found in Darwin, and no case of dengue has been reported in the Northern Territory since before 1949. No information suggesting endemicity in Western Australia appears in the literature; epidemics in the northern part of that State have usually corresponded with those in Darwin.

Of course, other factors beside temperature are necessary for endemicity. One is abundance of *A. ægypti*; over the years this has not been lacking in the north. Another is the continuing adequate supply of susceptible human hosts. The history of urban yellow fever, which is transmitted in the same way as dengue, provides an analogy. About 1920, it was observed that an urban population of about 50,000 was the usual minimum for endemicity without a steady influx of non-immune foreigners (Smith, 1951).

[1] In Townsville this was estimated at 75% in 1897 (Hare, 1898) and 37·5% in 1954 (Rowan, 1956).

In northern Australia such an urban concentration is approached only in Townsville (40,000) where, as already noted, a high attack rate belies endemicity. There might be considered also the combined urban and rural population of about 50,000 in the Cairns-Innisfail district. In past years these populations were much less. Assuming that the yellow fever observation may tentatively be applied to dengue, there would thus be hardly any centres in northern Australia populous enough for endemicity.

The argument based on minimum population was valid for yellow fever only where its transmission depended on the man-*ægypti* cycle. But yellow fever has also another cycle with non-human reservoirs and other mosquito vectors. If this should exist for dengue also, there would be a mechanism of endemicity (or enzooticity) independent of human participation. A further factor which may be relevant is the presence around Darwin and at Cape York of *Aëdes scutellaris*, which is a vector of dengue in New Guinea (Woodhill, 1949 ; Mackerras, 1946).

While there is thus no convincing evidence that dengue has ever been endemic in northern Australia, a final decision on this point must await the application of the specific tests now available.

ACKNOWLEDGEMENTS

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AORTIC VALVOTOMY FOR AORTIC STENOSIS : THE CLINICAL ASSESSMENT[1]

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SUMMARY

A clinical study of fifty consecutive cases of aortic stenosis has been made with the object of assessing their suitability for aortic valvotomy.

It is pointed out that severe symptoms develop late in the disease, and that at this stage operation may be an extremely hazardous procedure. Symptoms of severe effort dyspnœa, paroxysmal dyspnœa, *angina pectoris* and sometimes effort syncope are of grave prognostic significance irrespective of the patient's age. Early symptoms of moderate exertional dyspnœa, fatigue and consciousness of the heart's action in a patient with aortic stenosis should not be regarded too lightly. They should draw attention to the necessity for more careful study of the case by other methods, so that the need for operation or otherwise can be assessed at an early stage.

It is stressed that clinical and electrocardiographic signs often precede these symptoms and allow of early assessment. The pulse wave, assessed clinically and if necessary from an arterial pulse trace, is of important prognostic significance. A pulse pressure of 40 millimetres or below suggests severe aortic stenosis. Auscultatory signs are important in diagnosis but not so much in prognosis.

The importance of careful radiological study of each case is emphasized. The presence or absence of calcium in the valve and the degree of calcification are fundamental considerations in diagnosis and in the decision on surgical methods of treatment.

The presence and degree of left ventricular hypertrophy in the electrocardiogram is a vital consideration in all cases.

Hæmodynamic studies with calculation of the systolic gradient across the valve and technical assessment of the degree of aortic incompetence are mentioned as being of value in doubtful cases.

IT is almost a decade since the first modern mitral valvotomy was carried out simultaneously by Bailey in America and by Sir Russell Brock in England. One at first may wonder why it took eight and a half years for such intrepid and progressive surgeons successfully to deal with aortic stenosis, but a little thought will reveal several reasons.

The first is related to the position of the valve. There is no easily accessible auricular appendage through which to approach the valve as in mitral stenosis, but in aortic stenosis the approach has to be through the left ventricle or aorta.

Secondly there is the anatomical structure and function of the valve itself (MacMillan, 1955). The mechanism of valve opening is a more complicated procedure than in the case of the mitral valve, and in addition the predisposition to extensive calcification in the older age groups contributes to the difficulty of successful splitting even in autopsy specimens.

There is a third and perhaps more important reason, however, why successful aortic valvotomy has only comparatively recently become an established fact. It lies in the attitude of referring patients to the surgeon for aortic valvotomy too late with a resultant high mortality rate. This mortality rate has influenced physicians to consider operation only as a last resort, and so the late reference of patients for surgery and the high surgical mortality rate have been perpetuated.

REFERENCE OF CASES FOR SURGERY

It has been the practice in the past to teach that aortic stenosis becomes a serious disease only in the fourth and fifth decades of life, and that patients do not die from this disease in the early age groups. This is quite false, as is illustrated by the figures in 78 cases referred to Sir Russell Brock (1957) (see Table I). All these patients had severe symptoms, and their lives were in danger. Operation was urgently

[1] Received on November 22, 1957. Read at an ordinary meeting of The Royal Australasian College of Physicians in Sydney, October, 1957.

[2] Honorary Assistant Physician.

needed. The table shows that the patients were well distributed throughout the younger and middle, as well as the older age groups.

Aortic stenosis can be a killing disease, even in children, and Braverman and Stanley Gibson (1957) in a large series of over 70 cases found that there was an 8·2% mortality before the middle teens. Marquis and Logan (1955) found that five out of 28 patients in their series died before they reached the age of 20 years, four of these dying very suddenly.

Angina, effort syncope and severe dyspnœa are ominous symptoms in a child. The appearance of these symptoms has a serious significance, and it may be found that the patient is then in too advanced a state to withstand successful operation.

TABLE I

Age Groups of 78 Patients With Aortic Stenosis[1]

Age Group (Years)	Number of Patients
1–9	4
10–19	7
20–29	5
30–39	15
40–49	25
50–59	20
60–69	2

[1] Sir Russell Brock, 1957; reproduced by permission.

To understand why cases should be referred earlier it is necessary to look at the natural history of the disease.

Firstly, in mitral stenosis episodes such as rheumatic infection, pregnancy, bronchitis, auricular fibrillation and congestive cardiac failure may punctuate the downhill course to death over a period of years. In aortic stenosis the course from health to death is quite a different one. There is a long period in which the patient is more or less symptomless or has only mild symptoms. When the symptoms become severe, cardiac failure has already begun, and the course downhill is then a very steep one indeed.

Brock (1957) has put the situation picturesquely when he speaks of the left ventricle being like a willing horse. It goes on for years uncomplainingly working against the burden of the closed aortic valve and then suddenly it drops down dead.

SURGICAL METHODS

At the Cardio-Vascular Unit (St. Vincent's Hospital, Sydney) the indications for and contraindications against aortic valvotomy for aortic stenosis in 50 consecutive cases have been assessed.

Of the 50 patients, 28 were selected as suitable for operation. Three of them died suddenly from pulmonary œdema before operation could be carried out. Eighteen were recommended for early surgery and seven for later consideration, as it was felt that there was no immediate urgency for operation. Four of the 18 have been surgically treated. Three had transaortic valvotomy under direct vision, and one, a man of 56 years with heavy valve calcification, had his aortic valve dilated with retrograde approach through the ventricle.

It would seem that direct splitting under vision is preferable in the younger age group where the calcification of the valve is absent or minimal. Brock (1957) makes out a very convincing case, however, for retrograde dilatation through the ventricle in the older age group with heavily calcified valves. This procedure seems less hazardous in older subjects at present.

In expert hands the mortality rate for the combination of these two methods is about 8%, which is not high for a killing disease.

SYMPTOMATOLOGY

An attempt has been made to assess the cases firstly from the point of view of symptomatology. Of the 28 subjects, 23 had severe exertional dyspnœa, 14 had true *angina pectoris*, five had effort syncope, and in 19 fatigue was a prominent symptom. In 12 "palpitations" was a presenting symptom.

It is important to realize that *angina pectoris* in aortic stenosis is almost always due to the aortic stenosis; and far from being a contraindication, it may often be regarded as a cry from the heart for help for a better coronary circulation. Coronary filling is improved after successful valvotomy.

PHYSICAL SIGNS

The general appearance of most of the patients in this series was not remarkable. The typical "Dresden china look" was seen in only one case.

The pulse was most important in the assessment of aortic stenosis from both the diagnostic and prognostic viewpoints. In 18 subjects it was found to be anacrotic, and in two there was a bisferiens type of pulse. In both these latter cases there was considerable, if not predominant, incompetence.

In 13 subjects the pulse pressure was 40 mms. Hg or less—a very significant finding in assessing the severity of the stenosis.

The apex beat, although not displaced, was definitely heaving and left ventricular in type in 24 of the 28 subjects chosen for surgery.

There was a systolic murmur present in all the 28 subjects at the aortic area, and this systolic murmur was also heard in 26 subjects with lesser intensity at the mitral area. In all cases the murmur was accompanied by a palpable thrill at the aortic area, and in two cases the thrill was also felt at the mitral area.

In 10 cases there was an aortic diastolic murmur indicating some degree of aortic incompetence.

It is important to realize that an aortic diastolic murmur is not a contraindication to operation unless there are other signs of gross aortic incompetence. These signs include a left ventricle extending well out to the left clinically and radiologically and a large pulse pressure. If there is any doubt after full assessment, the aortic valve is explored. If there are minor or moderate degrees of aortic incompetence, it may even be improved by operation.

In two cases there was the mid-diastolic murmur of mitral stenosis, and these people had a combined valve lesion.

A systolic click was audible in five cases. Varied significance has been applied to this sign. Some claim that it is an ejection click in a heavily burdened left ventricle. Others say that it is associated with marked post-stenotic dilatation of the aorta. In the five cases in the series a moderate to well marked post-stenotic dilatation of the aorta was noted radiologically.

The character of the second aortic sound was significant in 21 cases. In six the aortic second sound was not heard, and in 15 it was greatly diminished in intensity. However, it is important to realize that the aortic sound may be perfectly normal or even louder than usual in aortic stenosis.

Radiology

Careful study of the radiological findings is essential in every case of aortic stenosis considered for operation. In the surgical series of 28 cases the left ventricle was enlarged radiologically in 23.

Left ventricular hypertrophy in pure aortic stenosis is usually of the concentric type.

If the left ventricle projects well out towards the left, giving a boot-shaped appearance to the heart, one may suspect that aortic incompetence is the predominant lesion. The presence or absence of calcification in the aortic valve is a fundamental consideration in all cases. It is as well to have definite evidence of calcium on an X-ray film or tomogram, as well as having the observations of an experienced cardiologist at the time of screening.

Calcium was present in 14 cases. In the nine cases in which it was not present the subjects were under the age of thirty years. Two patients had combined lesions.

In pure aortic stenosis the absence of calcification in a patient over thirty years of age should make the diagnosis subject to revision.

Functional left ventricular obstruction occasionally occurs in hypertensive patients.

Hypertrophy of the aortic outflow tract proximal to the valve may occur in such a way as to give rise to a type of infundibular chamber.

With this development clinical signs similar to those of aortic stenosis may appear and give rise to confusion in diagnosis, particularly as the blood pressure will now have fallen as a result of the partial obstruction.

Brock (1957) has recognized this condition and has shown how it can be diagnosed by left ventricular puncture and a withdrawal trace recorded through a catheter inserted through the valve and infundibulum.

There was post-stenotic dilatation of the aorta apparent in the postero-anterior film in six of the 28 cases. This aortic dilatation occurs perhaps more often in congenital aortic stenosis, but may occasionally occur in acquired cases. It usually, but not always, means a severe degree of aortic stenosis.

Electrocardiogram

Assessment from the electrocardiogram is fundamental. The rhythm is nearly always regular, and auricular fibrillation in pure aortic stenosis is said to occur in only 3% of cases. There was auricular fibrillation in two cases, and both the subjects had mitral valve disease; one had mitral stenosis and the other mitral incompetence, in addition to the aortic valve stenosis. When auricular fibrillation occurs in aortic stenosis, one should always suspect the coincidence of mitral valve disease.

Left ventricular hypertrophy was present in 22 of the 28 cases. This is a most important electrocardiographic sign. Most subjects who require operation will have left ventricular hypertrophy in their electrocardiogram, provided that there is not a coincident mitral stenosis.

On the grading of Sokolov and Lyon (1949), it is found that most subjects who require operation are in grade two to grade four—i.e. the majority but not all patients with aortic stenosis requiring operation have a considerable degree of left ventricular hypertrophy as determined electrocardiographically. The exercise test may

occasionally be helpful in doubtful cases. Ischæmic *S–T* depression changes in the left ventricular leads may be noted after exercise in a record which was normal with the subject at rest.

CONTRAINDICATIONS TO SURGERY

The main contraindications to aortic valvotomy may be listed as: firstly, a terminal state; secondly, gross aortic incompetence or other valve lesion more important than the aortic stenosis which is not amenable to surgery; thirdly, active rheumatic infection or subacute bacterial endocarditis.

When right-sided congestive heart failure due to aortic stenosis is established, the patient is beyond aid. Operation will almost certainly prove fatal. If the patient is getting attacks of paroxysmal cardiac dyspnœa, but is not in right-sided congestive cardiac failure, operation is worth consideration. When this stage has been reached in aortic stenosis, however, the hazards of operation are high. Retrograde dilatation of the valve is probably the safest procedure in these cases.

The second obvious contraindication is gross aortic incompetence. A wide pulse pressure and a large left ventricle, giving rise to a boot-shaped heart as seen radiologically, are commonly found when the degree of aortic incompetence is considerable. One must be careful, however, not to exclude patients purely because they have a diastolic murmur. Where there is doubt, the assessment by technical methods from data obtained at left ventricular puncture may be of value. If there is still doubt, the aortic valve should be explored.

Mitral stenosis occurring coincidently with aortic stenosis is not a contraindication to the operation. In these patients the left ventricle has been protected to some extent by the mitral stenosis, and the procedure of aortic valvotomy is even better tolerated than in pure aortic stenosis. Both valves should be split at the one operation; otherwise disability from a remaining valve lesion would be increased.

Mitral incompetence of more important degree than the aortic stenosis is, of course, a contra-indication to surgery.

The third contraindication is also an obvious one, and that is active infection, which may be rheumatic or associated with bacterial endo-carditis.

HÆMODYNAMIC STUDIES

In most cases of aortic stenosis one can assess the severity of the condition by a careful clinical study of the symptoms, signs and radiological and electrocardiographic findings as outlined above. There will be a certain number of cases in which the cardiologist will still find himself in doubt as to the severity of the disease. It is in these cases that hæmodynamic studies, carried out by percutaneous left ventricular puncture according to the technique of Fleming and Gibson (1957), will prove of great value.

This investigation was carried out in 17 cases of this series. With increasing experience it will not be necessary to carry out this procedure in such a high percentage of cases.

INDICATIONS FOR SURGERY

It is not yet possible to assess fully the results of operation, owning to the short time which has elapsed since the first aortic valvotomy. At this stage, however, the most important indications for operation appear to be: (*a*) Symptoms of progressive dyspnœa, angina and effort syncope. (*b*) Electrocardiographic evidence of severe left ventricular hypertrophy and strain with or without symptoms. (*c*) A low systolic blood pressure and small pulse pressure, and especially a prolonged upstroke time in the arterial pulse trace. (*d*) A high systolic gradient detected on left ventricular puncture.

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HÆMODYNAMIC STUDIES IN THE ASSESSMENT OF AORTIC STENOSIS[1]

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SUMMARY

Direct percutaneous puncture of the left ventricle has been performed on 17 occasions in 16 patients with aortic stenosis. It is a simple, repeatable procedure and causes no significant change in circulatory hæmodynamics. The systolic gradient, aortic valve area and brachial artery upstroke time were calculated by comparison with an immediately consecutive brachial artery record. A systolic gradient of 50 mm. Hg indicates a severe lesion, and moderately large gradients were found in patients with slight electrocardiographic changes. Further study is needed to decide the place of this investigation in the surgical assessment of aortic stenosis.

"FOR as one of the valve cusps is bony and the others indurated they become less yielding to the blood, obstructing its exit from the ventricle. Eventually these circumstances were bound to overload the heart and lungs." (Morgagni, 1762.) These words admirably sum up the eventual fate of the patient with aortic stenosis. This fate has led the cardiac surgeon to attempt to relieve this obstruction at the aortic valve. The decision as to which patients should have surgery causes both surgeon and physician constantly to ask: "When will this overload of the ventricle occur?"

Unfortunately right heart catheterization gives little or no information about the state of the left ventricle, and a study of the peripheral arterial pulse wave is informative but often indefinite. In 1953 Bjork *et alii*, and later Fisher (1955), introduced a posterior percutaneous puncture technique, but reports of the complications of this method caused most observers to doubt the justification of its use.

In 1956, Brock, Milstein and Ross suggested percutaneous direct left ventricular puncture through the intact chest wall. The basis of this technique is that a study at operation and autopsy of the line of the outflow tract of the left ventricle shows that it corresponds to a line drawn from the apex of the heart to the second right costo-chondral junction, and inclined backwards at an angle of about 35° to the sternum. The latter angle was calculated from a study of a line drawn from the apex through the centre of the area of valve calcification. It varied from 24° to 42° with a mean of 35° (Brock *et alii*, 1956). A needle inserted in this line has a better chance of entering the left ventricular chamber than one passing across the outflow tract, and there is less chance of damage to a coronary vessel since these are small in the region of the apex of the ventricle.

The patient is premedicated with "Omnopon", one-third of a grain, and scopolamine, one one-hundred-and-fiftieth of a grain, and lies supine. The procedure is performed in the operating theatre, and instruments are available for emergency thoracotomy, cardiac resuscitation and aortic valvotomy. An electrocardiograph is connected in every case, and a percutaneous brachial artery puncture is performed.

In four patients the right side of the heart was catheterized prior to this and the catheter left in the pulmonary artery so that the cardiac output could be estimated. More recently the cardiac output was estimated by a radioactive isotope dilution curve in six patients (Seldon *et alii*, 1957) (Figure I). The skin is prepared and the chest draped in the usual way, and the position of the apex beat and of the second right costo-chondral junction is then marked on the skin. The position of the apex is confirmed by the study of an antero-posterior radiograph of the chest. The skin about two centimetres below and lateral to the apex beat is infiltrated with local anæsthetic, and the infiltration carried down to the pericardium. The electrocardiogram is watched, and the appearance of one or two extrasystoles warns the surgeon that

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he has penetrated the myocardium. An 18-gauge needle 12·5 centimetres long is connected to the electromanometer and a heparin-saline solution run slowly through it. The needle is inserted a little below and lateral to the apex and directed towards the second right costo-chondral junction with a backward inclination of 35°. A small aluminium trowel is used to estimate this angle (Figure II). The needle is inserted until the ventricle is felt impinging on the needle tip, and it is then advanced into the ventricle (Figure III). A careful watch is kept on the electrocardiogram which shows a few extrasystoles (Figure IV). A pressure tracing is recorded, followed immediately by a brachial artery recording. A Y-piece with one-way taps was used to obtain this record. This procedure is remarkably simple and causes the

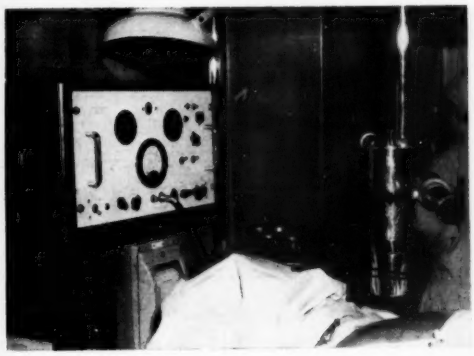

FIGURE I

Isotope method of estimating cardiac output with the scintillation counter over the second right intercostal space and a scaler and a recording apparatus at the head of the patient

patient no distress. An X-ray picture of the chest is taken immediately afterwards to exclude pneumothorax, hæmopleura and hæmopericardium.

This procedure was performed on 17 occasions in 16 patients. Minor complications have been : one short burst of ventricular tachycardia, one small hæmopericardium, a pericardial rub and pain in one patient's chest next day and mild syncopal attacks suffered by two patients at the end of the procedure. The last-mentioned responded to lowering the head of the table. During the procedure there were only slight alterations in the circulatory hæmodynamics. The blood pressure fell in seven cases, rose in five and was unchanged in five. The average alteration in the systolic pressure was 10 mm. Hg and ranged from six to 27 millimetres. The pulse rate rose in six patients, fell in six and was unchanged in five. The changes were mostly small, but in one patient the pulse rose from 90 to 140 per minute.

In this series there were eight men and eight women, with ages ranging from eight to 57

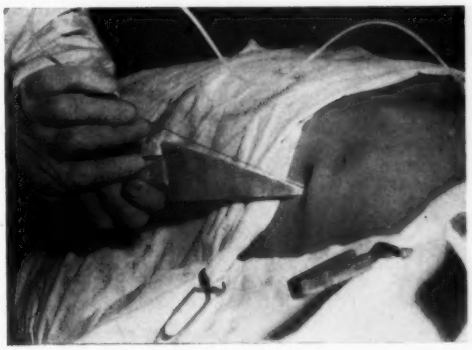

FIGURE II

Needle entering chest wall with a trowel marking an angle of 35° to the sternum

years. In all a diagnosis of aortic stenosis was made, and aortic valvotomy was under consideration. In seven an aortic diastolic murmur was present with or without other clinical evidence of regurgitation. One patient had

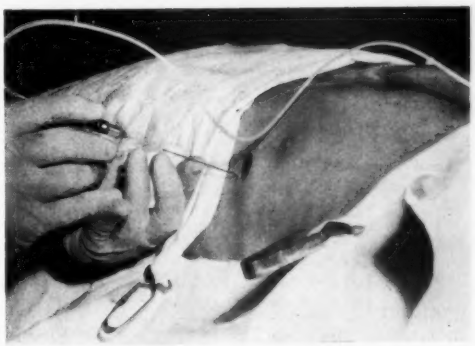

FIGURE III

Needle in the left ventricle

concomitant mitral stenosis, and one had coarctation of the aorta. Acceptable left ventricular pressure records were obtained in all cases (Figure V). The left ventricular pressure pulse shows the following features (Figure VI) : (i) that the early diastolic pressure was comparable with the pulmonary capillary

pressure and usually about 10 mm. Hg; (ii) that a small positive wave was almost constantly present just before the main upstroke of the left ventricle systole. This end diastolic pressure varied between 11 and 47 mm. Hg. It was unrelated to the presence of aortic incompetence, and in no patient was there clinical evidence of left ventricular failure at the

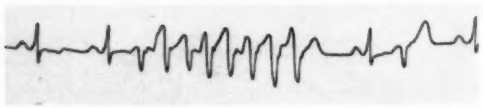

FIGURE IV

Ventricular extrasystoles as the needle pierces the myocardium. Needle into left ventricle

time of the examination. It was, on the whole, higher in those with the highest left ventricular systolic pressures but not necessarily those with the highest gradients; e.g., an end diastolic pressure of 47 mm. Hg was recorded in a patient with aortic stenosis, aortic incompetence and coarctation, whose left ventricular pressure was 253 mm. Hg but whose gradient was only 40 mm. Hg. In four patients there was a prominent "a" wave in the pulmonary capillary wedge tracing, but simultaneous pulmonary capillary and left ventricular records were not

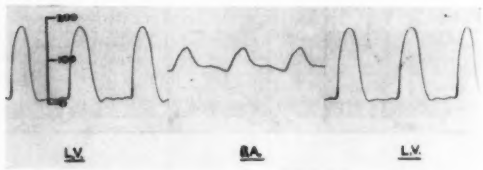

FIGURE V

Immediately consecutive left ventricular and brachial artery pressure tracings. The scale of pressures is in millimetres of mercury. One major horizontal division represents 0·2 second

performed. This feature has previously been noted by Musser *et alii* (1956) and by Fleming and Gibson (1957). The former suggest that it may be due to an alteration in the pressure volume relationship of the left ventricle. The most striking feature of the left ventricular dynamics is the development of a high systolic pressure, and pressures ranging from 153 to 272 mm. Hg were recorded with an average of 208 mm. Hg. The peak systolic gradient was obtained from a comparison of the left ventricular and brachial artery pressures and varied from seven to 152 mm. Hg (Table I). There was a general tendency for the gradients to be proportional to the severity of the electrocardiographic changes as graded according to Sokolow and Lyon (1949), but there were

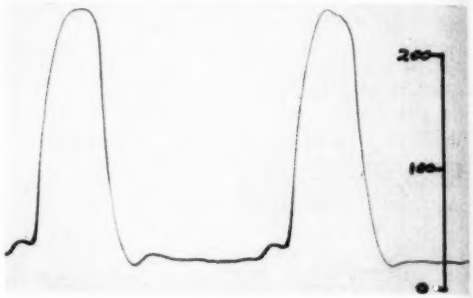

FIGURE VI

Left ventricular pressure pulse tracing showing the raised end diastolic pressure. The scale of pressures is in millimetres of mercury. One major horizontal division represents 0·2 second

exceptions (Figure VII). The results do not agree completely with Fleming and Gibson (1957), who claim that severe aortic stenosis cannot occur with a normal electrocardiogram.

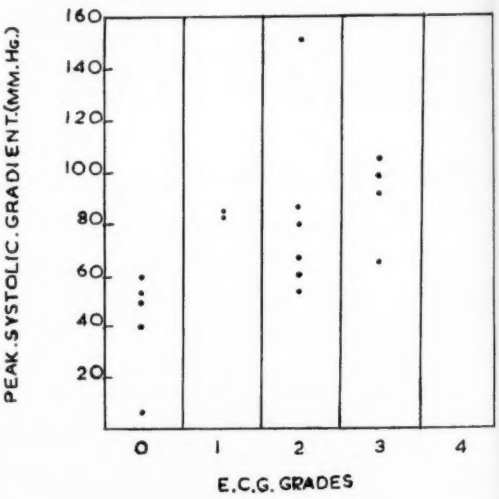

FIGURE VII

Peak systolic gradients grouped according to the severity of the electrocardiographic changes

One patient (case 14) with no electrocardiographic changes and a gradient of 60 mm. Hg, and two patients (cases 3 and 9) with grade one changes and gradients 84 mm. Hg and

Hæmodynamic Studies in 17 Patients with Aortic Stenosis

Case Number	Sex	Age (Years)	Diagnosis[1]	Electrocardiographic (grade of Left Ventricular Hypertrophy	Left Ventricle Pressure (mm. Hg)			Brachial Artery Pressure (mm. Hg)			Brachial Artery Systolic Upstroke Time (Seconds)	Measured/Normal Brachial Artery Upstroke Time	Peak Systolic Gradient (mm. Hg)	Mean Systolic Gradient (mm. Hg)	Left Ventricular Isometric Contraction Time (Second)	Left Ventricular Upstroke Time (Seconds)	Ejection Period (Second)	Measured/Normal Ejection Period	Pulse Rate	Cardiac Output (Litres/minute)	Aortic Valve Area Calculated (Square Centimetres)	Surgical Estimate of Valve Size
					Systolic	Mid-Diastolic	End-Diastolic	Systolic	Diastolic	Pulse Pressure												
1	F.	14	A.S., A.I.	2	240		27	153	86	67	0·16	1·6	87	43	0·03	0·18	0·26	1·04	100	7·6		
2	F.	47	A.S., A.I., M.S.	0	227		13	173	93	86	0·18	1·6	54	35	0·03	0·16	0·26	1·04	83			
3	M.	8	A.S., A.I.	1	177	13	20	93	60	33	0·22	2·0	84	43	0·03	0·16	0·28	1·2	100			
4	F.	37	A.S., A.I.	2	200	5	10	133	80	53	0·20	2·0	67	—	0·02	0·19	0·29	1·2	94			
5	F.	37	A.S., A.I.	2	272	10	20	120	66	54	0·26	2·4	152	115	0·03	0·20	0·36	1·4	83	3·5	0·39	
6	F.	58	A.S., A.I.	1	187		13	180	66	114	0·18	—	7	—	0·03	0·12	—	—	68			
7	M.	56	A.S.	2	200		10	120	63	57	0·22	2·1	86	66	0·04	0·20	0·34	1·4	88	4·0	0·31	
8	F.	12	A.S.	3	213		27	120	80	40	0·20	2·0	93	69	0·04	0·20	0·28	1·2	100	3·2	0·92	
9	M.	32	A.S., A.I.	1	213	20	40	127	66	61	0·23	1·9	86	55	0·02	0·14	0·30	1·1	75	6·8	0·44	
10	F.	18	A.S., A.I.	0	153	10	33	103	63	40	0·16	1·6	50	34	0·04	0·16	0·30	1·2	94	3·2	0·55	
11	M.	43	A.S., A.I.	3	220	—	30	113	66	47	0·22	2·4	107	87	0·03	0·18	0·24	1·1	125	6·8	0·60	0·60
12	M.	30	A.S.	3	227	—	33	127	73	54	0·20	2·0	100	80	0·02	0·18	0·32	1·3	88	6·7	0·60	0·40
13	M.	56	A.S.	3	187	13	20	127	67	60	0·24	1·8	67	55	0·04	0·24	0·36	1·1	34	3·2	0·61	
14	M.	50	A.S.	3	180	7	11	120	67	53	0·23	2·1	60	53	0·03	0·17	0·29	1·1	83			
15	M.	8	A.S., A.I., coarct.	2	253	26	47	200	93	107	0·16	1·4	53	—	—	—	—	—	79	—	—	
16	M.	35	A.S., A.I.	0	173	—	20	140	93	47	0·22	2·2	40	29	0·02	0·12	0·18	1·0	100	9·2	0·40	
17	F.	37		2	213	7	12	153	90	63	0·20	2·0	60	—	—	—	—	—	90	—	—	

[1] A.S. = aortic stenosis. A.I. = aortic incompetence. M.S. = mitral stenosis. Coarct. = coarctation.

86 mm. Hg were present in this series. Brock (1956) claims that a gradient of 50 mm. Hg is an indication for surgical therapy, and this was present in 14 patients. Much lower gradients are significant if the patient has mitral stenosis, but in one patient with a double lesion (case 2), a gradient of 54 mm. Hg was present. The ascending limb of the ventricular pressure tracing is interesting in that initially there is a slow phase of pressure rise. The pressure then rises rapidly, and in three patients there was a period on the upward slope when the rise in ventricular pressure became less rapid. This has been noted previously by Bakst *et alii* (1957). They suggest that this probably produces the anacrotic notch on the arterial tracing and that it appears as though the left ventricle pauses to take a " second breath ".

A comparison of the arterial and left ventricular pressure pulses enables the following measurements to be made (Fleming and Gibson, 1957): the isometric contraction time, which was generally abbreviated; the systolic ejection period, which was always prolonged, although the degree was no indication of the severity of the stenosis; and the left ventricular upstroke time or phase of rapid ejection, which was normal, but which Felming and Gibson found shortened. These measurements are interesting but of no diagnostic significance (Table I).

The aortic valve area was calculated in nine patients by the formula of Gorlin (1951). This formula makes allowance for both gradient and flow, which are obviously interrelated. Figures between 0·31 and 0·99 square centimetre were obtained. In two patients this was compared with the surgeon's estimate at operation, and in one both agreed at 0·6 square centimetre, while in the other 0·61 square centimetre was the calculated area, and the surgeon estimated the valve to be 0·4 to 0·5 square centimetre. Fleming and Gibson (1957) point out that this formula tends to over-estimate the size of the valve, but that it gives a reasonable estimate of the degree of aortic stenosis.

The arterial tracing was abnormal in all patients. The variation consisted of an interruption in the upstroke or a true anacrotic notch in nine (Figure VIII), a rounded top in four, a waterhammer pulse in two (Figure IX) and a bisferiens type of pulse in two (Figure X). The systolic upstroke time measured from the beginning of the upstroke to the peak of the tidal wave was considerably prolonged in all patients, and the increase appeared to be proportional to the gradient and electrocardiographic severity. The degree of pro-

longation, as compared with the expected normal (calculated from 1/p.r.) is an indication of the severity of the disease. It is usually twice in severe stenosis. The diastolic pressures which were recorded by arterial puncture were always lower than those recorded by indirect methods, often differing by 20 mm. Hg, although these measurements were not made simultaneously. The pulse pressures were therefore larger than is expected in aortic stenosis and varied between 33 and 88 mm. Hg in those with dominant aortic stenosis.

FIGURE VIII

A typical anacrotic pulse. The scale of pressures is in millimetres of mercury. One major horizontal division represents 0·2 second

The wisdom of using the brachial pressure as an indication of aortic pressure may be questioned. Burchell and Ward (1955) have shown that in normal people the brachial artery and femoral pressures are slightly higher than the aortic, and in aortic stenosis this difference is less marked (Wright *et alii*, 1956, Fleming and Gibson, 1957). However, there is a much greater increase in the peripheral systolic pressures in pure aortic incompetence (Wright *et alii*, 1956). A reference to the variation in a combined lesion could not be found. Aortic incompetence raises special difficulties, as the cardiac output estimated is the effective one and not the true flow, so that any calculated valve area will be an under-estimation. The radioactive method of estimating cardiac output is not any more accurate in this regard that the Fick method. Two patients with signs of aortic stenosis (thrill and loud murmur) and aortic incompetence had gradients of seven mm. Hg and 14 mm. Hg. This suggested that the latter was the dominant lesion. However, the opposite does not follow, and Fleming and Gibson (1957) have reported one case with a gradient of 100 mm. Hg and predominant incompetence. The presence of significant gradients with little or no electro-cardiographic changes in this series is contrary to the conclusion of Fleming and Gibson (1956), that severe aortic stenosis cannot occur with a normal cardiogram. It tends to favour the opposite conclusions of Matthews *et alii* (1955). This raises important questions. Do these patients have significant gradients from early life, and does this gradient increase as their condition deteriorates? At what stage should surgery be attempted, and does a measurement of the left ventricular pressure answer this question? Is surgery indicated in the presence of a significant gradient, electrocardiographic changes or both? These questions cannot be answered at present, but left ventricular puncture introduces an easily repeatable investigation whereby the changes in the form and height of the left ventricular pressure pulse can be correlated with the natural history of the disease.

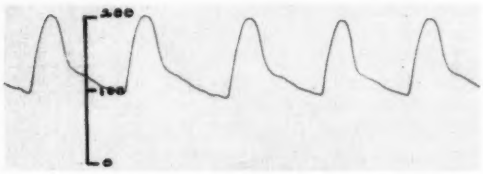

FIGURE IX

A typical waterhammer pulse. The scale of pressures is in millimetres of mercury. One major horizontal division represents 0·2 second

FIGURE X

A typical *pulsus bisferiens*. The scale of pressures is in millimetres of mercury. One major horizontal division represents 0·2 second

In conclusion, percutaneous left ventricular puncture is safe, causes only slight inconvenience to the patient and is repeatable. When compared with an immediately consecutive brachial artery record, the systolic gradient, aortic valve area and brachial artery systolic upstroke time can be calculated. These are the most useful measurements in assessing the severity of aortic stenosis. A systolic gradient of at least 50 mm. Hg indicates a severe lesion, and moderately large gradients were present in patients with slight electrocardiographic changes. The presence of aortic incompetence raises special

difficulties in the interpretation of the results. This investigation is most useful in the borderline case with early electrocardiographic changes and in those with associated aortic incompetence or other lesions. Further study is needed to see if this investigation will assist in assessing at which stage in the natural history of aortic stenosis surgery is indicated.

ACKNOWLEDGEMENTS

We wish to thank Mr. Harry Windsor and Mr. P. Heery, who were responsible for insertion of the left ventricular puncture needle. Our thanks are also due to the Department of Medical Illustration, St. Vincent's Hospital, for the preparation of the illustrations.

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MEGALOBLASTIC ANÆMIA ASSOCIATED WITH ANTICONVULSANT DRUG THERAPY[1]

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SUMMARY

An epileptic boy of 16 years developed megaloblastic anæmia while being treated with primidone and phenytoin. There was an optimal hæmatological response to folic acid therapy. Laboratory investigations showed a normal serum concentration of vitamin B_{12} and normal radioactive vitamin B_{12} absorption. This is the thirty-third reported case of megaloblastic anæmia associated with anticonvulsant therapy.

Certain features common to the majority of these cases suggest that a folic acid deficiency or a derangement of folic acid metabolism is responsible for the megaloblastic anæmia. All 20 patients treated with folic acid responded optimally. Eight patients are reported to have responded to vitamin B_{12}, one to liver extract and four to a combination of folic acid and vitamin B_{12}.

It is suggested that the anticonvulsant drugs have an antifolic acid action which is too mild to produce megaloblastic anæmia in the majority of epileptics unless one or more co-factors operate. A suboptimal folic acid intake is postulated as the main co-factor in at least five of the 20 cases in which there was a response to folic acid and perhaps also in some of the cases in which a response has been reported to vitamin B_{12}. In one case repeated hæmorrhage, in another pregnancy and in a third case a possible latent steatorrhœa are postulated as additional co-factors.

SINCE Badenoch (1954) reported the occurrence of megaloblastic anæmia in two young epileptic women on anticonvulsant drug therapy there have been a total of 32 such cases described: 27 from the United Kingdom, three from Sweden and one each from the United States of America and Italy.

A causal relationship between the anticonvulsant drugs phenobarbitone, phenytoin and primidone and the megaloblastic change in the bone marrow has been postulated, and Girdwood and Lenman (1956) drew attention to the general similarity in the molecular structure of these drugs and that of pteroylglutamic acid.

The anticonvulsant drugs taken by these patients within six months prior to the diagnosis of anæmia have been prescribed either singly or in various combinations (Table I). Megaloblastic anæmia was associated with single drug therapy with primidone in five cases (Nos. 18, 19, 23, 24 and 25), phenytoin in four (Nos. 3, 5, 7 and 22), and phenobarbitone in one (No. 12). Phenobarbitone was combined with phenytoin in 15 cases (Nos. 1, 2, 6, 8, 10, 11, 13, 14, 15, 20, 21, 26, 30, 31 and 32), with primidone in three (Nos. 16, 17 and 27), and with both phenytoin and primidone in four (Nos. 4, 9, 28 and 29).

The purpose of this paper is to review the published cases and to record a case of our own which we believe to be the first to be reported from Australasia.

CASE REPORT

On October 29, 1956, a 16-year-old mentally defective epileptic boy was referred to the Royal Perth Hospital because he appeared severely anæmic. For eight years he had been an in-patient of a mental hospital. He had been a violent and difficult patient to manage and had strong homosexual tendencies; however, his attendants had noticed that he was much more docile during the month prior to his referral. There was no history of blood loss, and the dietary history seemed quite adequate.

Since the age of three years this boy had been having minor and major epileptic attacks. During the years up to 1953 he had received at different times various forms of anti-epileptic drug therapy, which included phenobarbitone, "Tridione", sulphonal and "Rutonal". He developed skin rashes on several occasions, which were thought to be a manifestation of a drug sensitivity successively to "Rutonal" and phenobarbitone. In 1948 several attempts were made to administer lithium carbonate because he presented a very difficult behaviour problem; however, each attempt was unsuccessful because of severe complications such as albuminuria, gastritis and, in 1950, encephalitis.

In 1953 primidone, one gramme per day, was commenced, and in 1954 to this was added phenytoin

TABLE I
A Summary of the Main Features of the Reported Cases of Megaloblastic Anæmia Associated with Anticonvulsant Drug Therapy

[1] Received on December 2, 1957.
[2] Department of Hæmatology. In receipt of a grant-in-aid from The Royal Australasian College of Physicians.
[3] Honorary Physician.

TABLE I

A Summary of the Main Features of the Reported Cases of Megaloblastic Anæmia Associated with Anticonvulsant Drug Therapy

Author	Case No.	Sex	Age	Anticonvulsant Drugs During Past Six Months	Duration of Therapy	Gastric Analysis (Free Acid Present)	Serum Vitamin B_{12} (Milli-micro-grammes per Milli-litre)	Vitamin B_{12} Absorption	Fat Balance	Folic Acid Absorp-tion	Drug Withdrawn	Therapeutic Response	Possible Co-Factors
Badenoch, 1954	1	F.	22	Epanutin Phenobarbitone	—— ——	0 (Biopsy normal)	120	Normal	Normal	—	—	B_{12}	? Nutrition
	2	F.	17	Epanutin Phenobarbitone	—— ——	+ (Biopsy normal)	215	Normal	Normal	—	—	Folic acid	? Nutrition
Hawkins and Meynell, 1954	3	M.	52	Epanutin	13 years	+ (Biopsy normal)	—	—	Normal	—	—	Folic acid	——
Chalmers and Boheimer, 1954	4	M.	32	Phenytoin Phenobarbitone Mysoline	5 years Years 2 months	—	155	Normal	Normal	—	—	Folic scid	——
	5	F.	47	Phenytoin	——	0	—	—	—	—	—	B_{12}	——
Rhind and Varadi, 1954	6	F.	19	Phenobarbitone Phenytoin	Years 9 months	+	135	—	Abnormal three-day balance 58% absorbed	—	—	Folic acid	? Latent steatorrhœa
Webster, 1954	7	F.	23	Phenytoin	4 years	+	—	—	—	—	Yes	B_{12}	? Nutrition
Berlyne, Levene and McGlashan, 1955	8	M.	28	Phenytoin Phenobarbitone	18 months 18 months	+	—	—	—	—	No	Folic acid	—
	9	M.	26	Phenytoin Phenobarbitone Mysoline	4 years 4 years 3 months	+	—	—	—	—	No	Folic acid	——
Ryan and Forshaw, 1955	10	M.	32	Phenytoin Phenobarbitone	5 years 5 years	+	—	—	—	—	Yes	B_{12}	? Nutrition
	11	F.	28	Phenytoin Phenobarbitone	8 years 8 years	+	—	—	—	—	Yes	Folic acid	——
	12	F.	27	Phenobarbitone	——	—	—	—	—	—	—	B_{12} and folic acid	——
Vaishnava, 1955	13	F.	28	Phenytoin Phenobarbitone	2 years ——	+	—	—	Normal	—	—	Folic acid	——
	14	F.	23	Phenytoin Phenobarbitone	2 years ——	+	—	—	—	—	—	Folic acid	Pregnancy
Hurwitz, 1956	15	F.	19	Phenytoin Phenobarbitone	8 years 8 years	0	—	—	Normal	—	No	B_{12}	——
Girdwood, 1956	16	F.	41	Phenobarbitone Mysoline Phenobarbitone Mysoline	Years 6 months 17 months 17 months	+	— 160	—	—	Normal —	Yes —	Folic acid Folic acid	Nutrition
		Relapse											
Girdwood and Lenman, 1956	17	F.	42	Phenobarbitone Primidone	7 months 7 months	+	—	—	—	Normal	No	Folic acid	——

TABLE I—(*Continued*).

A Summary of the Main Features of the Reported Cases of Megaloblastic Anæmia Associated with Anticonvulsant Drug Therapy—(Continued).

Author	Case No.	Sex	Age	Anticonvulsant Drugs During Past Six Months	Duration of Therapy	Gastric Analysis (Free Acid Present)	Serum Vitamin B_{12} (Milli-microgrammes per Milli-litre)	Vitamin B_{12} Absorption	Fat Balance	Folic Acid Absorption	Drug Withdrawn	Therapeutic Response	Possible Co-Factors
Fuld and Moorhouse, 1956 ..	18	F. Relapse	37	Primidone Primidone	4 months 7 months	+	— —	Normal Normal	Normal —	— —	Yes No	Folic acid Folic acid	Nutrition
	19	F.	44	Primidone	2 years	+	—	—	Normal	—	Reduced	Folic acid	Nutrition
Gydell, 1957	20	F.	48	Diphenylhydantoin Phenobarbitone	13 years 13 years	+	230 220	—	—	—	Yes	B_{12}	Nutrition Recurrent hæmorrhage
	21	F.	26	Diphenylhydantoin Phenobarbitone	2 years 2 years	+	—	—	—	—	No	B_{12}	Nutrition
	22	F.	39	Diphenylhydantoin	7 years	+	—	—	—	—	Yes	Liver extract	Nutrition
Newman and Sumner, 1957 ..	23	F.	52	Primidone	2 years	+	—	—	Normal	—	No	Folic acid	——
	24	F.	49	Primidone	1 year	+	—	—	Normal	—	Yes	B_{12}	Nutrition
Christenson, Ultmann and Roseman, 1957	25	F. Relapse	48	Primidone Primidone	2 years 8 months 1 year 2 months	+	— —	— —	— —	— —	Yes No	Nil. Diet unchanged Folic acid	Nutrition
Forshaw, 1957	26	F.	60	Phenobarbitone Phenytoin	1 year 1 year	+	—	—	—	—	Yes Phenytoin	Folic acid	Nutrition
Volterra and Romauldi, 1957 ..	27	M.	33	Phenobarbitone Primidone	Years 5 years	+	—	—	—	—	—	Folic acid	——
Benians and Hunter, 1957 ..	28	F. Relapse	29	Phenobarbitone Phenytoin Primidone Phenobarbitone Phenytoin	3 years 3 years 2 years 1 year 8 months 1 year 8 months	+ +	— —	— —	— —	— —	Primidone —	Folic acid —	—— ——
	29	M.	25	Primidone Phenytoin Phenobarbitone	Greater than 10 months 6 months	+	—	—	—	—	Yes Phenytoin and primidone	B_{12} and folic acid	——
	30	F.	51	Phenytoin Phenobarbitone	4 years 4 years	+	—	—	—	—	Yes Phenytoin	B_{12} and folic acid	——
Barker, 1957	31	M.	36	Phenobarbitone Phenytoin	20 years 4 years 6 months	+	—	—	—	—	No	Folic acid	——
	32	F.	35	Phenobarbitone Phenytoin	4 years 4 months 2 years 2 months	—	—	—	—	—	No	B_{12} and folic acid	——
Present authors — —	33	M.	16	Primidone Phenytoin	3 years 2 years	+	145	Normal	—	Normal	Yes Primidone	Folic acid	——

sodium, 0·2 gramme per day. When any further sedation was necessary he received paraldehyde orally. He was receiving this therapy at the time of admission.

Physical examination revealed a well developed boy of 16 years, who was very pale. There was no abnormality of his tongue or gums. There was no evidence of any bleeding tendency, and the result of a Hess test of capillary fragility was normal. The regional lymph nodes were not enlarged, and the liver and spleen were not palpable. Examination of the nervous system, the cardio-vascular system and the respiratory system failed to reveal any abnormality.

Laboratory Data

The hæmoglobin value was 5·3 grammes *per centum*. The erythrocytes numbered $1 \cdot 3 \times 10^6$ per cubic millimetre. The packed cell volume was 17%, and the mean corpuscular volume 131 c.μ. The reticulocyte content was 1·7%. The leucocytes numbered 3,500 per cubic millimetre and the platelets 168,000 per cubic millimetre. The bone marrow was hypercellular. Erythropoiesis was intensely megaloblastic, and many of the megaloblasts were primitive. Some giant metamyelocytes were present.

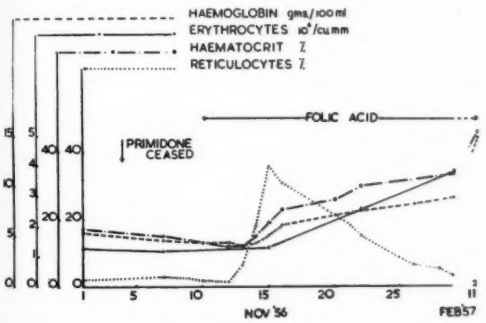

FIGURE I

The hæmatological response of the present patient (Case 33) to folic acid therapy

The presence of free acid in the gastric juice was demonstrated by a fractional test meal. The serum vitamin B_{12} concentration estimated by the microbiological assay method of Ross (1952), using *Euglena gracilis*, was 145 millimicrogrammes per millilitre. This value falls within the normal range for this laboratory. The absorption of radioactive vitamin B_{12}, using a modified 48-hour urinary excretion test (Pitney and Stokes, 1957), was normal. Radioactivity amounting to 17·4% of an oral dose of 0·6 microgramme of ^{60}Co B_{12} was excreted in the urine over 48 hours. A fat balance was unsuccessful through lack of co-operation of the patient, who ate very little during the period of investigation. The result of a glucose tolerance test was normal, and the absorption of folic acid was also normal, as measured by the folic acid excretion test of Girdwood (1953). The total serum protein content was 6·2 grammes *per centum* (albumin 3·8 grammes and globulin 2·4 grammes). The serum calcium content was 9·6 milligrammes per 100 millilitres (normal 9–11·5 milligrammes per 100 millilitres), and the serum iron content prior to treatment was 280 microgrammes per 100 millilitres (normal for males 80–175 microgrammes per 100 millilitres).

In an endeavour to determine which drug was responsible for the megaloblastic anæmia it was intended to withdraw each drug in turn while continuing with the other. We chose to withdraw primidone first, and this was ceased on November 4, 1956. Eight days later there had been no rise in the reticulocyte count. On November 10, 1956, it was considered unsafe to continue with the period of controlled observation, as the hæmoglobin value had fallen to 4·4 grammes *per centum*, and the packed cell volume had fallen to 13%. Therefore folic acid, 20 milligrammes given daily by mouth, was commenced (Figure I). An optimal reticulocyte response of 36% occurred on the fifth day after commencing folic acid. The red cell and hæmoglobin values rose steadily and were normal three months later.

Folic acid was ceased after five months (April 24, 1957). The patient has since been maintained on phenytoin sodium and phenobarbitone for a further five months without relapse occurring.

DISCUSSION

Thirty-two cases of megaloblastic anæmia associated with anticonvulsant drug therapy have been reported since 1954, our case being the thirty-third. The phenomenon is therefore not common, particularly when compared with the large number of epileptics who are being treated with these compounds.

Berlyne, Levene and McGlashan (1955), Ryan and Forshaw (1955) and Gydell (1957) re-investigated 75, 102 and 54 epileptics respectively on maintenance therapy without finding a single case of megaloblastic anæmia, while the two cases reported by Newman and Sumner (1957) were drawn from a total of 176 epileptics treated with primidone from 1953 to 1955 inclusive. Benians and Hunter (1957) searched the records of a mental hospital with over two thousand patients during the four-year period 1953–1956 and found only three patients who they considered had a megaloblastic anæmia due to anticonvulsant and sedative drugs alone.

The drugs which have been associated with the anæmia in these cases have been phenobarbitone, phenytoin and primidone, either alone or in various combinations. Hobson, Selwyn and Mollin (1956) have also reported the occurrence of megaloblastic anæmia associated with barbiturate therapy. Their patient was a 30-year-old female, who was a manic depressive but not epileptic, and who was addicted to large doses of a mixed barbiturate preparation "Tuinal". This patient was similar to the majority in this series in that she had free acid in the gastric juice, normal serum vitamin B_{12} concentration, normal vitamin B_{12} absorption and no evidence of malabsorption of folic acid or fat, and responded to folic acid.

Before considering the relationship between the anæmia and the drug therapy in the reported cases, the possibility of some of those affected being epileptics who have developed an

Addisonian pernicious anæmia, quite unrelated to the drug therapy, must be kept in mind. It seems possible that the second case reported by Marshall, Chalmers and Boheimer (1954) (Case 5) was such a case, although the diagnosis of pernicious anæmia was not proven.

This 47-year-old epileptic woman, who had been taking phenytoin, had histamine-fast achlorhydria. There were signs of neurological damage, and she responded hæmatologically to parenteral administration of vitamin B_{12}.

Most authors have postulated either a direct or an indirect causal relationship between these drugs and the megaloblastic change in the bone marrow, although to date the underlying mechanism resulting in megaloblastic erythropoiesis is obscure. There are certain features common to the majority of these cases which suggest that a folic acid deficiency or a derangement of folic acid metabolism is responsible for the megaloblastic anæmia.

Age and Sex Incidence

The average age of the patients in the 33 cases is 34·4 years. The oldest patient was aged 60 years and the youngest aged 16 years. In 15 cases (46%) the patients were below the age of 30 years, and in four cases (12%) they were below 20 years of age. This age incidence differs greatly from that found in pernicious anæmia. In a total of 1532 cases of pernicious anæmia drawn from six large surveys, Davis (1944) found only four cases (0·3%) in patients under 20 years of age. The sex incidence in this series is 24 females to nine males.

Gastric Analysis

Free acid was present in the gastric juice of 27 patients (82%), three had histamine-fast achlorhydria (cases 1, 5 and 15), and in three no test meal was performed. Gastric biopsy was carried out on three patients (Nos. 1, 2 and 3) and was described as normal in each case. Of the three patients with histamine-fast achlorhydria, one (case 1) was one of the three shown to have normal gastric mucosa by gastric biopsy; another (case 5) possibly has pernicious anæmia, while a third (case 15) was a 19-year-old female with spontaneous hypoparathyroidism. Normal gastric physiology therefore is a feature of the majority of the cases.

Absence of Neurological Involvement

Clinical evidence of neurological involvement was absent in all except three cases (Nos. 5, 24 and 32). The patient in case 5 has been mentioned already as possibly having pernicious anæmia. The patient in case 24, who complained of dysæsthesia of the feet and calf tenderness, seems likely to have had peripheral neuritis. As this patient was stated to have had a poor diet for 10 years, it is not unreasonable to postulate a vitamin B_1 deficiency as the probable cause of the neurological lesion. Although the absence of deep reflexes in all limbs of the patient in case 32 remains unexplained, it appears that neurological damage is not a feature of the megaloblastic anæmia associated with anticonvulsant drugs.

Folic Acid Metabolism

Response to Folic Acid.—Twenty patients in this series (cases 2, 3, 4, 6, 8, 9, 11, 13, 14, 16, 17, 18, 19, 23, 25, 26, 27, 28, 31 and 33) were treated with folic acid, and in every case a good hæmatological response followed. The folic acid was administered orally in a dose varying from 15 to 45 milligrammes daily in 19 of these cases, and one patient (No. 27) was given the drug intramuscularly at a dose of 15 milligrammes on alternate days. In seven of these cases (Nos. 3, 4, 6, 8, 16, 17 and 27) the patients had failed to respond to conventional doses of vitamin B_{12}.

Hæmatological response followed combined treatment with folic acid and vitamin B_{12} in four cases (cases 12, 29, 30 and 32). As the serum vitamin B_{12} concentration was not assayed in any of these four cases, there is no evidence to indicate whether the patients responsed to vitamin B_{12} or folic acid. In cases 29 and 30 the patients secreted free acid in their gastric juice and therefore in this respect are similar to the majority of the patients in this series. As no test meal was performed in cases 12 and 32, the patients have been insufficiently investigated to exclude the diagnosis of pernicious anæmia, although their ages of 27 and 35 years respectively make this diagnosis unlikely.

The similarity of the clinical features of the majority of these cases to those occurring in the "folic acid deficient" megaloblastic anæmias and their invariable response to folic acid have prompted some to suggest that the causal relationship between the anticonvulsant therapy and the anæmia is through an antifolic acid action of the drugs. That this is a direct causal relationship is demonstrated by case 25.

A 48-year-old epileptic female had been on a poor diet for years, was anorexic and had a glossitis at the time of diagnosis. Eight days after ceasing primidone therapy she developed a reticulocyte response of 16%, which was followed by an hæmatological remission. No folic acid or vitamin B_{12} was given, and her diet, although poor, was not altered. Fourteen months after recommencing primidone therapy the patient relapsed and on this occasion responded to folic acid without the withdrawal of primidone.

The mechanism of the antifolic acid action of these drugs is uncertain. On theoretical grounds they could interfere with folic acid metabolism by inhibiting the absorption of pteroylglutamic acid and its conjugates from the food, by increasing urinary excretion of folic or folinic acid, or by blocking the metabolism of these substances in nucleoprotein synthesis. Folic acid absorption was measured by the method of Girdwood (1953) in four cases (Nos. 16, 17, 26 and 33) and was found to be normal in each case. In only one case (No. 17) was this test performed while the patient was still on the anticonvulsant drug therapy. Girdwood and Lenman (1956), having drawn attention to the general similarity in the molecular structure of pteroylglutamic acid, phenobarbitone, primidone and phenytoin, suggested that the last two substances may, under certain circumstances, successfully compete with folic acid as a co-factor in the synthesis of nucleoprotein. Case 12 and the case of Hobson, Selwyn and Mollin (1956) suggest that phenobarbitone may also act in this way.

While no conclusions can be made concerning the nature of the antifolic acid action of these drugs, there is no evidence of a malabsorption syndrome. A fat balance investigation was carried out in 12 cases (Nos. 1, 2, 3, 4, 6, 13, 15, 18, 19, 23, 24 and 26), and the result was normal in all except case 6. In this case the patient had a three-day fat balance, which indicated that 54% of dietary fat was being absorbed. In seven other cases (Nos. 7, 9, 10, 11, 14, 20 and 22) fat absorption was reported as being normal on the basis of an isolated fæcal fat estimation.

Vitamin B_{12} Metabolism

A serum vitamin B_{12} assay was performed when the patient was in hæmatological relapse in only seven cases (Nos. 1, 2, 4, 6, 16, 20 and 33) and was normal in all. The ability to absorb orally administered vitamin B_{12} was measured in four (Nos. 1, 2, 4, and 33) of these seven patients and was also found to be normal in each case. Evidence of normal vitamin B_{12} metabolism in a further 15 cases may perhaps be inferred from the fact that the response to folic acid was adequate and sustained; in one of these cases (No. 17) the patient had a normal serum vitamin B_{12} level three months after responding to folic acid.

A total of eight patients were reported to have responded to vitamin B_{12} and one to liver extract. In two of these cases (Nos. 1 and 20) the serum vitamin B_{12} content had been estimated and found to be normal. In the first case, one of the two original cases reported by Badenoch (1954), the patient had a low normal serum vitamin B_{12} value of 120 millimicrogrammes per millilitre. It is not stated whether the anticonvulsant drug had been withdrawn prior to vitamin B_{12} therapy, or whether conventional or large doses of vitamin B_{12} were used in treating this patient. In the second case (No. 20) the patient was reported to have responded to 100 microgrammes of vitamin B_{12}.

This 48-year-old epileptic female had been taking phenobarbitone and diphenylhydantoin for 13 years. Diphenylhydantoin therapy was ceased four months before the diagnosis of megaloblastic anæmia was made. At that time she had a fever and felt tired. Her hæmoglobin value was 62%, her erythrocyte count was $2 \cdot 5 \times 10^6$ per cubic millimetre, and she had a leucopenia of 1500 per cubic millimetre. This patient had pronounced mental deterioration. She had felt tired and become anorexic at least nine months before the megaloblastic anæmia was discovered, and had had repeated severe uterine bleeding which had necessitated an hysterectomy. When examined she was apathetic. There was scattered purpura over her body, with increased capillary fragility, and vitamin *C* unsaturation was demonstrated. There was evidence of glossitis and gingival hypertrophy. The pre-treatment serum vitamin B_{12} concentration was 230 and 220 micromilligrammes per millilitre. No hæmatological response occurred to vitamin *C* after 16 days, although the purpura had ceased and the capillary fragility had become normal. On the seventeenth day, vitamin B_{12} therapy was begun at a dose of 100 microgrammes per day. This was followed by a 17·6% reticulocyte response six days later. Three months later the blood count was normal, and in this time the patient had gained seven kilograms in weight.

The response to vitamin B_{12} in patients with a normal serum vitamin B_{12} concentration is at present unexplained. Mollin and Ross (1954) have indicated that there are a few patients with severe megaloblastic anæmia with low normal pre-treatment serum vitamin B_{12} levels who respond suboptimally and incompletely when large doses of vitamin B_{12} are given. The large doses referred to are in the vicinity of 1000 microgrammes. This effect is possibly one of " mass action " and is not comparable to the full response to the conventional dosage of 100 microgrammes reported in some of the patients treated with vitamin B_{12}. An alternative explanation may be that the response to vitamin B_{12} is apparent rather than real. In case 20 the patient did not show clinical signs of malnutrition, although it seems possible that this patient was undernourished with respect to vitamin *C* and folic acid. If this were so, the hæmatological response which occurred on the twenty-second day after admission may perhaps have resulted from the improved folic acid intake since the hospital diet was taken.

In a further six cases (Nos. 5, 7, 10, 15, 21 and 24) the patients were reported to have responded to vitamin B_{12} therapy and one (case 22) to liver extract. In none of these had the serum vitamin B_{12} concentration been determined. Although the nature of the disturbance of vitamin B_{12} metabolism in these cases is not known, it is possible that the response in some was apparent rather than real. As already mentioned above concerning case 20, it would appear that in some of these cases the patients responded as a result of the improved folic acid intake occurring in hospital, together with the cessation of the antifolic acid action of the anticonvulsant drug when this drug was withdrawn. Case 22 is such a case :

A 39-year-old female with free acid in her gastric juice had been taking a poor diet. She had ulcerative stomatitis and gingivitis which caused pain on eating. The erythrocyte count at the time of diagnosis was $2 \cdot 3 \times 10^6$ cubic millimetres and the hæmoglobin value 56%. The anticonvulsant drug was withdrawn, and she was treated with liver extract together with vitamin *C* and a multi-vitamin *B* preparation. Although no significant reticulocyte response occurred, the hæmoglobin value had increased to 87% after one month.

It is noteworthy that in these nine cases in which there was response to vitamin B_{12} or liver extract, the diet was poor, and the patients had signs of undernutrition and/or mental deterioration and ulcerative stomatitis in six cases (Nos. 1, 7, 20, 21, 22 and 24). One patient (case 5) has already been referred to as possibly having pernicious anæmia. Of the remaining two, the patient in case 10 was stated to have had an adequate diet, although he was a 32-year-old male weighing only eight stone one pound, and had ulcers on both legs ; and in case 15, in which there is no mention of the diet, the patient had an associated spontaneous hypoparathyroidism with retardation in skeletal development. The anticonvulsant drug most likely to have been responsible for the megaloblastic anæmia had been withdrawn prior to the vitamin B_{12} therapy in five of these nine cases (Nos. 7, 10, 20, 22 and 24).

The rarity of megaloblastic anæmia occurring in epileptics on anticonvulsant drug therapy suggests that the antifolic acid action of the drugs is too mild to cause the anæmia in most cases unless one or more co-factors operate at the same time. Reference has been made by others (Gydell, 1957 ; Newman and Sumner, 1957) to the possibility of an inadequate diet being a causative factor in the disturbance of folic acid metabolism in the majority of the patients. Other possible co-factors are increased demand for red cell production occasioned by repeated blood loss, such as occurred in case 20, mild or latent steatorrhœa with impaired folic acid absorption, possibly illustrated by case 6, and pregnancy, as in case 14.

A diet may be suboptimal in folic acid but adequate in other respects, so that signs suggestive of undernutrition may not be present. It has been shown that the folic acid content of foodstuff decreases with storage in light and at room temperature in a comparatively short time (Olson, Burris and Elvehjem, 1947) and under some conditions is considerably reduced by cooking (Hanning and Mitts, 1949). It is reasonable therefore to suspect a suboptimal folic acid intake in any person who refrains from eating correctly cooked fresh deep greens and other foods with a high folic acid content, whether it be through fadism, through mental depression with anorexia, through pain on eating from ulcerative stomatitis and glossitis, or from eating overcooked "institutional" meals lacking in these commodities. Even in a community where the standard of living is high, folic acid-deficient megaloblastic anæmia may be common (Stokes, in preparation), in particular occurring in the old age pensioner and the alcoholic groups. It is suggested that the same situation pertains in some epileptics, for any of the above reasons, in whom a mild antifolic acid action of the anticonvulsant drugs is also active.

This thesis is supported by a consideration of the 33 cases under discussion. The high incidence of undernutrition in the nine patients reported to respond to vitamin B_{12} or liver therapy has already been mentioned. Of the remaining 24 patients, it has been mentioned that 20 responded to folic acid and four to combined folic acid and vitamin B_{12} therapy. Of these the diet was stated to be normal in seven cases (Nos. 4, 8, 9, 11, 17, 31 and 33), poor in five (Nos. 16, 18, 19, 25 and 26) and possibly inadequate in one (case 2). The diet was not mentioned in 11 cases, in one of which the patient was 7 months pregnant (case 14).

That increased demand for red cell production may operate as a co-factor is suggested by the fact that of the 33 patients in this series, 24 (73%) were females ; 17 of these 24 were in the menstrual age group of 17 to 45 years. There were four patients (Nos. 16, 18, 25 and 28) who relapsed after recommencing the anticonvulsant drug therapy and/or ceasing folic acid : all these patients were females, and three of the four were in the menstrual age group ; the fourth (case 25) was 48 years old.

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ADDENDUM

Since this paper was submitted for publication a report of three further cases has come to notice, making a total of 36 cases now on record. The two cases of Kidd and Mollin both had serum vitamin B_{12} concentrations as low as 40 micromilligrammes per millilitre. It seems likely that the vitamin B_{12} deficiency was due to a grossly inadequate diet in each case. One patient appeared to be suffering from a deficiency of both vitamin B_{12} and folic acid, and failed to respond to a treatment of vitamin B_{12} alone. Complete hæmatological response followed the administration of folic acid. This patient secreted free acid in the gastric juice, absorbed vitamin B_{12} normally, and had no evidence of malabsorption syndrome. The second patient died before the underlying deficiency could be clearly defined. However, blood taken at autopsy indicated severe vitamin B_{12} deficiency. Pernicious anæmia was excluded by the finding of a normal gastric mucosa; and although intestinal malabsorption was not excluded, the authors concluded that her condition was probably similar to that found in the first patient.

In addition to dietary deficiency, both patients had had added demands placed on their erythropoietic system prior to the manifestation of the megaloblastic anæmia. The first patient suffered from scorbutic gingival hæmorrhage and purpura, and the second from intractable menorrhagia of one month's duration necessitating hysterectomy.

A further case described by Bucher and Mangold appeared to respond to vitamin B_{12} therapy.

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DIAGNOSTIC VALUE OF RADIOACTIVE VITAMIN B_{12}[1]

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SUMMARY

The intestinal absorption of orally administered radioactive vitamin B_{12} has been studied by a modified urinary excretion test. Subjects were given a standard oral dose of 0·6 microgramme of ^{60}Co vitamin B_{12}. The mean 48-hour urinary radioactivity in 22 control individuals was 23·9% of the oral dose. In five patients with megaloblastic anæmia due to folic acid deficiency, a similar mean excretion of 22·4% was found. In 15 patients with pernicious anæmia in relapse, impaired absorption of radioactive vitamin B_{12} was demonstrated. The mean urinary radioactivity was 2·4%. This was increased to 19·6% when the oral dose was given with an intrinsic factor preparation.

Twenty-five patients on maintenance therapy because of a previous diagnosis of pernicious anæmia were studied. The diagnosis was disproved in 10 patients, who were shown to be able to absorb orally administered radioactive vitamin B_{12} normally.

THE biosynthesis of vitamin B_{12} labelled with a radioactive isotope of cobalt (Chaiet, Rosenblum and Woodbury, 1950) made possible the study of the absorption of physiological amounts of the vitamin in humans. Heinle, Welch, Scharf, Meacham and Prusoff (1952) used radioactive vitamin B_{12} to show that patients with pernicious anæmia absorbed the orally administered vitamin poorly unless an intrinsic factor preparation was given at the same time. Over the past few years many investigators using different techniques have confirmed these observations and have indicated the value of radioactive vitamin B_{12} in establishing the clinical diagnosis in patients suffering from megaloblastic anæmia, either in relapse or in remission following therapy.

The absorption of radioactive vitamin B_{12} can be demonstrated in several ways. Heinle and co-workers measured the radioactivity excreted in the fæces of their patients for several days after an oral dose of the vitamin. The difference between administered and excreted radioactivity represented that which was absorbed. The fæcal excretion technique has been used also by Callender, Turnbull and Wakisaka (1954*a*), Baker and Mollin (1955), and Halsted, Lewis, Hvolboll, Gasster and Swendseid (1956). All workers showed a clear distinction between the ability of patients with pernicious anæmia and normal individuals to absorb vitamin B_{12} from the gastro-intestinal tract. Even though the pernicious anæmia patient had been treated for many years and was in hæmatological remission, the absorptive defect remained. Such patients absorbed radioactive vitamin B_{12} normally if the dose was given with human gastric juice or an intrinsic factor preparation from hog stomach or duodenum. Patients who had undergone total gastrectomy behaved like pernicious anæmia patients in this test (Callender, Turnbull and Wakisaka, 1954*b*; Ley and Sharpe, 1954). The fæcal excretion technique is accurate, but time-consuming, and requires sustained cooperation on the part of the patient, as the loss of a critical fæcal specimen invalidates the test. Usually the patient must be confined to hospital during the investigation.

Glass, Boyd, Gellin and Stephanson (1954) placed isotope counting apparatus over the liver area of patients after oral administration of radioactive vitamin B_{12}, and demonstrated higher liver counts in normal subjects than in patients with pernicious anæmia. They used this as a test for measurement of intestinal absorption of vitamin B_{12}. The method has the disadvantages that several days must elapse before maximum liver activity is obtained, measurements cannot be made accurately until all unabsorbed radioactivity is excreted from the intestine, and it is difficult to quantitate the results obtained.

The recent introduction of radioactive vitamin B_{12} of high specific activity has made it possible to measure plasma radioactivity several hours after the oral administration of the vitamin (Booth and Mollin, 1956; Doscherholmen and Hagen, 1957). This is a convenient test of absorption which is likely to have future wide

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application when material of high specific activity becomes generally available.

Schilling (1953) introduced a rapid clinical test to detect the absorption of radioactive vitamin B_{12}. When a small oral dose of radioactive vitamin B_{12} is absorbed from the intestine, little or no radioactivity appears in the urine. However, if a large parenteral injection of non-radioactive vitamin B_{12} is given to the patient at the same time, or a few hours after the oral radioactive dose, radioactivity appears in the urine together with most of the injected vitamin. The urinary radioactivity excreted in 24 hours is usually about one-third of absorbed radioactivity (Callender and Evans, 1955), and its measurement may be taken as an index of absorption from the intestine. The urinary excretion test has been used extensively to study problems associated with megaloblastic anæmia and seems the most satisfactory at present for clinical work. The test as ordinarily described takes only 24 hours, radioactive vitamin B_{12} of low specific activity can be used, and measurement of urinary radioactivity is a relatively simple technical procedure.

In this paper we describe our experiences with a modification of the urinary excretion test. A number of patients with megaloblastic anæmia in relapse have been studied. The test has also been applied to the reevaluation of patients on maintenance therapy because of a previous diagnosis of pernicious anæmia.

METHOD

Radioactive vitamin B_{12} labelled with ^{60}Co and with specific activity of 0·24 microcurie per microgramme has been used in most tests. Recently material with a higher specific activity of 1·34 microcuries per microgramme has become available and is now in routine use. Mollin and Baker (1955) showed that in some subjects the secretion of intrinsic factor in the gastric juice could be stimulated by an injection of the parasympathetic stimulant "Carbachol" (carbamylcholine chloride). A preliminary injection of "Carbachol" is given in our modification of the urinary excretion test to ensure maximal intrinsic factor secretion.

The patient fasts for at least four hours prior to the test. Fifteen minutes before the radioactive vitamin is administered, an intramuscular injection of 0·25 milligramme of "Carbachol" is given. A standard dose of 0·6 microgramme of ^{60}Co vitamin B_{12} in 10 millilitres of water is then drunk, and immediately afterwards the patient is given an intramuscular injection of 1000 microgrammes of non-radioactive vitamin B_{12}. All urine passed over the next 24 hours is collected. The patient is then given a second intramuscular injection of 1000 microgrammes of vitamin B_{12}, and a second 24-hour urine collection is obtained. The second urine collection is carried out because Ellenbogen, Williams, Rabiner and Lichtman (1955) showed that appreciable radioactivity may be excreted in the urine on the second day if another large parenteral injection is given at the end of 24 hours.

Radioactivity of 100 millilitre samples of urine is measured using an ERD annular-type scintillation counter. The urine is placed in an annular aluminium container surrounding a cylindrical crystal of thallium-activated sodium iodide. The counter is connected to an EKCO Electronics Ltd. Type N530C automatic scaler. The counting apparatus employed gives counts of approximately 4000 per minute per 0·1 microcurie of ^{60}Co when measured in a 100-millilitre volume. Background counting rates range from 48 to 60 counts per minute. The scintillation counter is calibrated each time it is used against a permanent standard of ^{60}Co vitamin B_{12}. Each urine sample is counted for a minimum period of 10 minutes. Urinary radioactivity is expressed as a percentage of administered radioactivity.

If the measurement of urinary radioactivity indicates that the patient has absorbed subnormal amounts of the dose of radioactive vitamin B_{12}, the test is repeated using a mixture of the standard dose and 50 milligrammes of intrinsic factor concentrate. This intrinsic factor preparation (Lederle Batch, 186–1) at a dosage of 50 milligrammes is effective in increasing the absorption of a test dose of 0·6 microgramme of radioactive vitamin B_{12} in patients with pernicious anæmia. The material is from the same batch as that used by Baker and Mollin (1955) and Williams, Ellenbogen, Rabiner and Lichtman (1956) in their studies.

RESULTS

The results of the urinary excretion test in normal control individuals and in patients with megaloblastic anæmia in relapse are shown in Table I. The 22 normal controls were chosen from hospital patients with no evidence of blood or renal disease. Radioactivity of the first 24-hour urine collections ranged from 9·0% to 29·2% of the oral dose. Mean radioactivity excreted was 16·8%; standard deviation 4·8%. In all subjects a further parenteral injection of non-radioactive vitamin B_{12} was given 24 hours after the oral dose and urine collected for a further 24-hour period. Radioactivity excreted

TABLE I

Results of Radioactive Vitamin B_{12} Urinary Excretion Tests in Normal Controls and Patients with Megaloblastic Anæmia

Subjects	Number	Percentage of Administered Radioactivity Excreted		
		0—24 Hours	24—48 Hours	Total 0—48Hour Excretion
Normal controls	22	9·0—29·2 Mean 16·8 (S.D. 4·8)	3·1—11·3 Mean 7·1 (S.D. 2·2)	15·9—35·9 Mean 23·9 (S.D. 5·7)
Patients with megaloblastic anæmia (folic acid deficiency)	5	9·9—23·2 Mean 15·3	4·6—11·3 Mean 7·1	16·9—34·5 Mean 22·4
Patients with pernicious anæmia in relapse	15			
(a) Without intrinsic factor		0—4·1 Mean 1·3	0—3·1 Mean 1·2	0—7·2 Mean 2·4
(b) With intrinsic factor		6·9—19·8 Mean 13·3	3·8—9·9 Mean 6·3	11·1—29·0 Mean 19·6

in the second 24 hours ranged from 3·1% to 11·3%. Mean excretion was 7·1%; standard deviation 2·2%. The total 0 to 48-hour excretion ranged from 15·9% to 35·9% (mean 23·9%; standard deviation 5·7%).

The urinary excretion test was carried out on five patients with megaloblastic anæmia in relapse due to folic acid deficiency. The diagnosis of folic acid deficiency was established on the findings of a macrocytic anæmia associated with megaloblastic erythropoiesis on bone marrow examination and a normal serum vitamin B_{12} level estimated by a microbiological method using *Euglena gracilis* as test organism (Ross, 1952). All patients responded optimally to folic acid therapy. The cause of the deficiency in four patients was nutritional; the fifth patient suffered from megaloblastic anæmia of pregnancy. The test was performed immediately after the reticulocyte peak had been passed subsequent to folic acid therapy. Radioactivity of the first 24-hour urine collections ranged from 9·9% to 23·2% (mean, 15·3%). The second 24-hour excretion ranged from 4·6% to 11·3% (mean, 7·1%). The total 0 to 48-hour excretion ranged from 16·9% to 34·5% (mean, 22·4%). These figures are very similar to those shown by the normal controls.

Fifteen patients were examined with the urinary excretion test who were suffering from pernicious anæmia in relapse. These patients showed megaloblastic erythropoiesis on bone marrow examination, a low level of serum vitamin B_{12} concentration and histamine-fast achlorhydria. The radioactive test was carried out immediately after the reticulocyte peak had been passed subsequent to an injection of 100 microgrammes of vitamin B_{12}.

Radioactivity of the first 24-hour urine collections ranged from 0 to 4·1% (mean, 1·3%) and of the second 24-hour urine sample from 0 to 3·1% (mean, 1·2%). The total 0 to 48-hour excretion ranged from 0 to 7·2% (mean, 2·4%).

The test was repeated in these 15 patients after an oral dose of 0·6 microgramme of ^{60}Co vitamin B_{12} mixed immediately before administration with a suspension containing

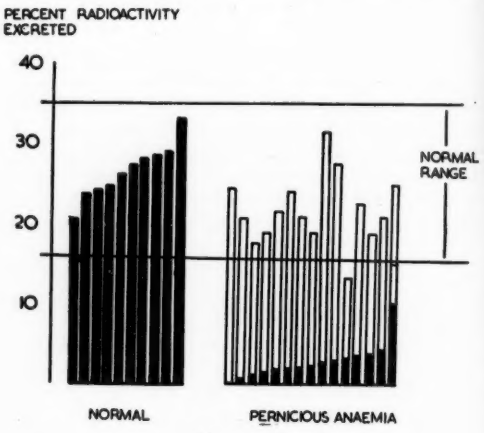

FIGURE I

Results of 0 to 48-hour urinary excretion tests in 25 patients on maintenance therapy because of a previous diagnosis of pernicious anæmia. Urinary radioactivity when the dose was given without intrinsic factor is indicated by the black columns. The augmented excretion in patients with pernicious anæmia after the administration of intrinsic factor is indicated by the white columns. The patient represented by the column on the extreme right excreted 10% of administered radioactivity when the dose was given without intrinsic factor; 15% with 50 milligrammes of intrinsic factor; and 25% with 100 milligrammes of intrinsic factor.

50 milligrammes of intrinsic factor concentrate. In all patients, urinary radioactivity was considerably increased. Radioactivity in the 0 to 24-hour urine collections ranged from 6·9% to 19·8% (mean, 13·3%), and in the

24 to 48-hour collections from 3·8% to 9·9% (mean, 6·3%). The total excreted radioactivity in the 48-hour period ranged from 11·1% to 29·0% (mean, 19·6%).

The urinary excretion test has been performed on 25 patients who had been receiving maintenance therapy for pernicious anæmia for periods of up to 10 years. They were referred to us for reevaluation of the diagnosis. All patients had normal blood counts. The 0 to 48-hour urinary radioactivity percentages are shown in Figure I. Ten patients excreted normal amounts of radioactivity (between 16% and 36% of administered radioactivity), although the radioactive vitamin B_{12} dose was given without the addition of intrinsic factor. These patients were therefore secreting endogenous intrinsic factor normally and did not have pernicious anæmia. The remaining 15 patients excreted subnormal amounts of radioactivity (0 to 10%). In these patients the test was repeated with a mixture of radioactive vitamin B_{12} and 50 milligrammes of intrinsic factor concentrate. In all, urinary excretion was considerably increased, and in 13, excretion was in the normal range. In the remaining two patients, excretion values of 13% and 15% were obtained. In one of these patients, the test was repeated using 100 milligrammes of intrinsic factor concentrate, and a clearly normal result was then obtained.

DISCUSSION

Megaloblastic anæmia is not a complete diagnosis in itself; the nature of the deficiency, whether vitamin B_{12} or folic acid, must be ascertained, and the cause of the deficiency established. The most satisfactory method at present available to determine the nature of the deficiency in megaloblastic anæmia is the estimation of the serum vitamin B_{12} concentration (Stokes, 1958). Failing facilities for this investigation, the patient may be given a single injection of 100 microgrammes of vitamin B_{12} and the reticulocyte count followed. If the patient is vitamin B_{12}-deficient, a reticulocyte peak will be observed, usually on the sixth or seventh day after injection. The therapeutic trial with vitamin B_{12} is not without difficulties, however, as we have repeatedly observed reticulocyte responses in patients suffering from nutritional megaloblastic anæmia due to folic acid deficiency who have received no therapy except hospitalization and an adequate diet. To be effective, the therapeutic trial with vitamin B_{12} should not be commenced until the patient has been under observation for at least 10 days. This control period is often not possible when the clinical condition of the patient gives rise to anxiety.

If facilities do not exist for serum vitamin B_{12} estimations, the probable nature of the deficiency in a patient with megaloblastic anæmia can be inferred from the results of radioactive vitamin B_{12} absorption tests. Patients with folic acid deficiency absorb radioactive vitamin B_{12} normally. A patient with nutritional vitamin B_{12} deficiency will also absorb the orally administered radioactive vitamin normally. However, dietary vitamin B_{12} deficiency is excessively rare in Australia, and megaloblastic anæmia associated with a normal radioactive vitamin B_{12} absorption test is almost certainly due to folic acid deficiency. If there is inability to absorb orally administered radioactive vitamin B_{12}, the test should be repeated using intrinsic factor. If absorption is improved with intrinsic factor, the patient suffers from deficiency of endogenous intrinsic factor secretion, and this is the defect seen in pernicious anæmia. This type of result is also found following total gastrectomy. Failure to absorb the vitamin B_{12}-intrinsic factor complex is a feature of one type of malabsorption syndrome. Failure to absorb orally administered radioactive vitamin B_{12} has also been reported in patients with gross abnormalities of the gastrointestinal tract. Stagnant blind loops following short-circuit operations are especially prone to give rise to vitamin B_{12} deficiency.

The patient who has been receiving vitamin B_{12} injections for years for supposed pernicious anæmia creates a problem in management, as often the original diagnosis of pernicious anæmia was made on totally inadequate grounds. In some of these patients a histamine test meal will demonstrate free acid in the gastric juice, making the diagnosis of pernicious anæmia most unlikely. Many otherwise normal adults have histamine-fast achlorhydria, however, and the finding of achlorhydria is of little value in confirming or excluding the diagnosis of pernicious anæmia in such individuals. One approach has been to stop therapy with vitamin B_{12} and to observe the blood count over the ensuing months. If a patient with pernicious anæmia has been treated adequately, a surprisingly long time may elapse before anæmia develops after cessation of therapy. We have recently investigated a man in whom vitamin B_{12} therapy was stopped two years ago. The hæmoglobin content of his blood is normal, but the blood film shows mild macrocytosis. The serum vitamin B_{12} concentration is low, and radioactive studies confirm that he suffers from pernicious anæmia. Prolonged cessation of

therapy in a patient who does have pernicious anæmia exposes him to the possibility of neurological complications.

In this type of problem, the radioactive vitamin B_{12} absorption test gives a quick and satisfactory result. Of 25 patients investigated by this test 10 were shown not to have pernicious anæmia.

The urinary excretion test has some disadvantages compared to other techniques for determining radioactive vitamin B_{12} absorption. Excretion is dependent upon renal function, and low excretion values may be obtained in patients suffering from renal insufficiency (Miller, Corbus and Sullivan, 1957). These workers also found low values in patients suffering from acute infections. It is probable that there is a temporary depression of intrinsic factor secretion in acute infections, and the low excretion values were due to poor absorption of radioactive vitamin B_{12}. It is likely that other vitamin B_{12} absorption tests would also show abnormal findings in patients with infections.

An objection to the urinary excretion test is the undesirability of giving patients large intramuscular flooding injections of vitamin B_{12}. In the reevaluation of patients in hæmatological remission, this is not important; in patients suffering from megaloblastic anæmia, the parenteral injections constitute a form of therapy which may obscure the results of a therapeutic trial. For this reason, we have not performed the test in our patients with megaloblastic anæmia until after the reticulocyte peak has been passed.

A variable percentage of absorbed radioactivity appears in the urine after large parenteral injections of vitamin B_{12}. The mean fraction of absorbed radioactivity excreted in 84 patients tested by Callender and Evans (1955) was 34%, with a standard deviation of 6·4%. Apart from this variation between individuals, the same subject does not excrete a constant fraction of absorbed radioactivity on repeat testing (Mollin and Baker, 1955). Because of this variability, the fæcal excretion technique is the more reliable method for quantitative measurements.

The great advantage of the urinary excretion test is its convenience and simplicity. The procedure can be carried out on out-patients, and the result of the test is known rapidly. Although we routinely collect urine for 48 hours and have confirmed the observation of Ellenbogen and co-workers that considerable radioactivity may be excreted on the second day, the 48-hour test has not been any more useful in diagnosis than the 24-hour test. In most instances, therefore, patient cooperation is essential for only a 24-hour period. Ellenbogen (1957) has occasionally encountered patients who excrete considerably more radioactivity on the second day than the first day. The 0 to 48-hour test has proved of value in the diagnosis of these " delayed excretors ". For this reason we propose to continue with the 0 to 48-hour test as a routine procedure.

In the series reported in this paper, there has been no overlap in the excretion figures of normal individuals and patients with pernicious anæmia. The lowest 48-hour excretion recorded in a normal subject was 15·9%, and the highest in a patient with pernicious anæmia was 10%. This patient was in remission from previous therapy. It is likely, however, that as more patients are investigated with this test, some overlapping of ranges will be observed. It has been shown that the defect in intrinsic factor secretion in pernicious anæmia may not be complete, and probably all grades of deficiency exist. The range of intrinsic factor secretion in patients with pernicious anæmia is possibly continuous with the lower limit of the normal range. The routine use of " Carbachol " to stimulate intrinsic factor secretion may be of value in more clearly delineating the normal from the abnormal. Mollin and Baker (1955) using the fæcal excretion test found overlap between results from normal controls and patients with pernicious anæmia when the radioactive vitamin B_{12} was given without a preliminary injection of " Carbachol ". When the individuals in question were retested after " Carbachol " administration, absorption was found to be increased in the normal group but unaffected in the patients with pernicious anæmia.

Most of the tests reported in this paper have been carried out with ^{60}Co vitamin B_{12} of specific activity 0·24 microcurie per microgramme. The oral dose has been 0·6 microgramme containing 0·14 microcurie. Even were this radioactivity completely absorbed, roughly one third is excreted in the urine, so that maximum body retention from any one test has been about 0·1 microcurie. With the higher specific activity material now in use, the body burden may be about 0·5 microcurie. Little is known of the ultimate fate of the retained radioactivity. Radioactivity can be detected in the livers of patients some months after vitamin B_{12} absorption tests, so that excretion is unduly slow. The physical half-life of ^{60}Co is 5·3 years, and it would be desirable to use radioactive vitamin B_{12} labelled with isotopes of cobalt having a shorter half-life. ^{56}Co and ^{58}Co

vitamin B_{12} are both available, but their half-lives of about 70 days are too short for convenient use in Australia. ^{57}Co has a physical half-life of 270 days. At present vitamin B_{12} labelled with ^{57}Co should be the most satisfactory material to use for absorption tests in this country. However, there are technical difficulties associated with its production which limit the supply for diagnostic use.

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GOODPASTURE'S SYNDROME
(PULMONARY HÆMORRHAGE ASSOCIATED WITH GLOMERULONEPHRITIS)[1]

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SUMMARY

Nine cases, which show a combination of pulmonary hæmorrhage and glomerulonephritis, have been recorded: as the ætiology of the condition is obscure, brevity and precedence are urged to justify the name "Goodpasture's syndrome".

Only twelve other cases could be collected from the literature, but this probably does not reflect its real frequency.

The pulmonary lesions appear to be produced by some derangement of the humoral mechanisms of the body, similar to that operating in uncomplicated glomerulonephritis or related conditions, and are distinct and different from the pulmonary changes seen in the lungs in uræmia.

The renal lesion is predominantly glomerular and widespread; in most cases, the change is proliferative with hyaline change in the late stages. Active organization with giant-cell formation is a feature of some cases.

The lung changes are characteristically congestion and thickening of alveolar walls with some disintegration and rupture. Alveoli contain a cellular exudate; in later stages organization occurs.

Usually the first manifestation of the syndrome is hæmoptysis; and as there may be only a trace, or even no albumin in the urine, early diagnosis may be exceedingly difficult. This may influence or mask the real prognosis of the syndrome. As it is a killing disease of young adults, it deserves further study.

IN the course of a study of the pulmonary lesions of influenza, immediately after the first World War, W. E. Goodpasture described the illness of a young man of eighteen years:

"The second case was a more unusual one, being the only instance of its kind observed by us, and I have not seen a similar one described."

He was "admitted . . . with a typical attack of influenza . . . Afterward he at no time felt well . . . His cough persisted; he" gradually "lost weight". After one month he returned to hospital "with cough, pain in the chest, bloody sputum, anemia, and signs of bronchopneumonia in the right lower lobe . . . He expectorated quantities of bright red blood. The pneumonia speedily became massive and spread to the left lung . . . He died three days after admission . . . Urine showed a trace of albumin."

At post-mortem examination, in the lungs, "Hemorrhage instead of edema was the prominent feature . . .".

"Microscopically, . . . Alveoli and terminal bronchioles are filled with erythrocytes. There are innumerable foci composed of polymorphonuclears, fibrin, large mononuclear cells and disintegrating hyaline material . . . These foci often indicate small areas of necrosis of the alveolar walls. Here and there alveoli are filled with plugs of fibrin. In certain areas there is a great abundance of hyaline material upon the walls of the dilated alveolar ducts and in alveoli . . . In certain alveoli the exudate has undergone organization . . . Both larger and smaller bronchi appear normal . . . The spleen on section shows numerous foci of necrosis occupying especially the areas of former Malpighian bodies. Necrotic cells, polymorphonuclears, strands and networks of fibrin compose these areas, situated about the small arteries. The kidneys show a glomerular nephropathy with a fibrinous exudate in Bowman's capsule and cellular proliferation of glomerular tufts; some urinary tubules are filled with erythrocytes." (Goodpasture, 1919).

This appears to have been the first description of a striking clinical syndrome in which glomerulonephritis is complicated by severe idiopathic pulmonary hæmorrhage.

Much earlier (Goodhart, 1879) there is an account of a little girl with scarlatinal dropsy and hæmoptysis, but the pathological appearances were those of bilateral apical pneumonia.

Other cases of the syndrome have been recorded much more recently: two cases were presented for discussion at clinico-pathological conferences (Case Records of the Massachusetts General Hospital, 1948; Clinico-Pathological Conference No. 21, 1954) and seven cases from the Mayo Clinic have been recorded as examples of "hemorrhagic and interstitial pneumonitis with nephritis" (Parkin *et alii*, 1955). Necrosis of small arteries was present in four of these seven cases, and in the case from Hammersmith

[1] Received on December 9, 1957.
[2] Demonstrator in Pathological Histology.
[3] Lecturer in Pathology.

Hospital (Clinico-Pathological Conference No. 21, 1954). In a more detailed description of one of their cases (Edwards *et alii*, 1954), Parkin and his co-authors cite a report of two other cases (Coll, 1951).

It seems preferable to distinguish the syndrome by the name of its discoverer, rather than by some cumbersome descriptive alternative. As six of seven cases from the Mayo Clinic were followed over a four-year period, and as seven of the nine cases comprising this report have presented since 1955, it is improbable that the medical literature reflects the true frequency of this syndrome; sporadic cases are either not recognized or not recorded. Incidentally it is important that this condition should be clearly differentiated from pulmonary lesions associated with uræmia.

CASE HISTORIES

Case I

J.S., a builder's labourer, aged 21 years, was admitted to hospital on June 28, 1955. Ten days before, he had noticed tightness across his chest and persistent small hæmoptyses. Though tired and breathless, he continued to work. Then followed night sweats, vomiting and eventually an epididymitis. Apart from a small hæmoptysis, one year previously, he had been in good health. He was pale and breathless, and his blood pressure was 160/80 mm. Hg. The percussion note was impaired over the right lower lobe, and fine crepitations were heard over both lungs. The left epididymis was firm, nodular and tender; his urine contained one-eighth albumin.

His hæmoglobin value was 6·3 grammes *per centum*, and his white cell count was 10,000 per cubic millimetre with 80% of neutrophils. A chest film showed coarse mottling of both lungs, more obvious in the lower zones. Pathogens could not be cultured from his sputum. He was given penicillin and streptomycin and a slow blood transfusion.

Hæmoptysis continued, and about 24 hours after admission to hospital he became much more breathless, slightly cyanosed and shocked, and he died suddenly some four hours later.

Pathological Findings.—The right lung weighed 1110 grammes and the left 1250 grammes; they were indurated, bulky and dark red in colour. The right kidney weighed 220 grammes and the left 260 grammes; they were swollen, œdematous and congested. On microscopic examination the thickened alveolar walls are infiltrated with polymorphonuclear leucocytes; some have disintegrated. The alveoli are filled with red cells, macrophages and fibrin; a few contain fluid and white cells. There are some areas of early fibroblastic proliferation. The alveolar ducts are dilated, and often lined by a hyaline membrane. In most glomeruli there is structureless eosinophilic material. They show various degrees of endothelial proliferation, crescent formation and inflammatory cell infiltration; a few contain giant cells. Some are completely hyalinized. Others retain their capsular space. Around the more damaged glomeruli there is a fine mesh reticulum containing inflammatory cells and a few fibroblasts. The walls of a few small arteries and arterioles are swollen and eosinophilic. The veins of the epididymis are thrombosed and œdematous.

Case II

I.W., a 45-year-old dentist, was admitted to hospital on July 26, 1955. Three weeks previously he had had fever, sore throat and yellow sputum, but had worked intermittently for two weeks, despite some small hæmoptyses, until his urine became blood-stained. At this point his blood pressure was 150/90 mm. Hg; his blood urea content was 60 milligrammes per 100 millilitres. A chest film showed haziness and fine mottling spreading out from both hila. He was given streptomycin and penicillin. Four days later he became very breathless and was found to be anuric. He was pale and short of breath; percussion note and breath sounds were diminished, and there were numerous fine crepitations at the lung bases. Microscopic examination of the urine showed three pus cells and ten red cells per high power field and a few granular and epithelial casts. The hæmoglobin value was 6·8 grammes *per centum*; the white cell count was 20,000 per cubic millimetre with 93% of neutrophils. The blood urea content had risen to 140 milligrammes per 100 millilitres; the serum electrolytes were normal. His chest film showed dense, confluent and widespread mottling in both lungs, particularly in the lower zones. He continued to cough tenacious bloody sputum, his breathlessness increased, peripheral circulatory failure developed, and he died suddenly within 24 hours of admission.

Pathological Findings.—The right lung weighed 1520 grammes and the left 1390 grammes; they were dark red and solid to the touch and contained very little air. The right kidney weighed 260 grammes and the left 240 grammes; both were swollen, and the surfaces were smooth and spotted by tiny foci of congestion and hæmorrhage. On microscopic examination, some alveolar walls have broken down, and others are outlined mainly by small collections of leucocytes. The alveoli contain red cells, macrophages and fibrin; there are areas of recently formed fibrous tissue and collapsed alveoli. The glomeruli show extensive proliferation of the cells of the tuft, inflammatory cell infiltration, crescent formation and a few foci of necrotic eosinophilic material and giant cells. Around many glomeruli are wide zones of supporting tissue carrying a few damaged tubules and inflammatory cells. The walls of some arterioles are swollen and deeply eosinophilic.

Case III

H.K., a railway worker, aged 21 years, was admitted to hospital on November 30, 1955. Some 14 days previously he had brought up a large quantity of blood and a smaller amount the night before admission. He had remained at work after his first symptoms appeared. His blood pressure was 150/60 mm. Hg; his hæmoglobin value was 7·5 grammes *per centum*. His urine contained no albumin. Transfusion was begun, and his condition appeared satisfactory. Some eight hours after admission to hospital he began to cough a little bloody tenacious sputum; he was pale and became very breathless and apprehensive. A triple rhythm could be heard, with fine crepitations at his lung bases posteriorly. The transfusion was stopped; digoxin and morphia were given. He seemed to improve, but died suddenly three hours later. He had received no chemotherapy.

Pathological Findings.—The right lung weighed 1100 grammes, the left 900 grammes; both failed to collapse and showed small points of consolidation in a lobular distribution. The kidneys were swollen and pale and the glomeruli prominent. On microscopic examination alveolar walls are widened with prominent lining cells and, in places, approximated or broken down,

their boundaries outlined by intraalveolar leucocyte collections. The alveolar contents are red cells, hæmosiderin-carrying macrophages and scattered polymorphonuclear leucocytes. The alveolar ducts are dilated and contain fibrin, red cells and leucocytes. The glomeruli show endothelial proliferation and prominent basement membranes. Some tufts are adherent to their capsules; in others, tiny crescents are beginning to form. The interstitial tissue of the heart is œdematous and contains a few round cells.

Case IV

E.H., a typist, aged 16 years, was admitted to hospital on November 17, 1951. One month before, she had had influenza and a sore throat. Ten days before, swelling of her face and ankles had been followed by hæmoptysis and vomiting. She was pale and breathless, her face was puffy, and her ankles were swollen. Her blood pressure was 150/110 mm. Hg, and a presystolic triple rhythm could be heard. There was impairment of percussion note and fine crepitations were heard over both lower lobes. Her urine contained two-third albumin, red and white blood cells and casts. Her hæmoglobin value was 9 grammes *per centum* and her white cell count was 25,000 per cubic millimetre with 81% of neutrophils.

The chest film showed considerable mottled opacity through both lungs.

The patient continued to cough bloody sputum and became more breathless and cyanosed. She then began to bring up copious, frothy, blood-stained sputum, and early on the morning of the fourth day she collapsed and died.

Pathological Findings.—The right lung weighed 1110 grammes, the left 770 grammes; they were reddish-pink, and fluid could be expressed, leaving solid lung behind. The right kidney weighed 220 grammes, the left 225 grammes. The perirenal tissues were œdematous. The kidneys were enlarged and firm and the surfaces smooth. On microscopic examination, the alveolar walls were thick, with prominent lining cells, and infiltrated by polymorphonuclear leucocytes. Some alveoli contained degenerating red blood cells, but many more contained fibrin, macrophages or fluid; there were a few small collections of leucocytes. The terminal bronchioles and alveolar ducts were lined by a striking hyaline membrane. The glomeruli are swollen and ischæmic, showing cellular proliferation, increased lobulation and leucocytic infiltration. There are few crescents, and the capsular spaces persist. In some places tubules have been replaced by loose supporting tissue with a few inflammatory cells.

Case V

A.M., aged 41 years, was admitted to hospital on November 16, 1956. Ten weeks before he had suddenly vomited a large amount of blood or blood-stained fluid. Four weeks later he began to cough small amounts of blood-streaked sputum, especially in the mornings. He next suffered malaise, tiredness and increasing shortness of breath. His blood pressure was 150/80 mm. Hg. His urine contained one-fourth albumin. His hæmoglobin value was 6·2 grammes *per centum*, and the white cell count was 10,000 per cubic millimetre with 70% of neutrophils. His blood urea content was 270 milligrammes per 100 millilitres. His anti-streptolysin titre was 1 : 50. The bone marrow smear and platelet count were normal. His chest film showed moderate enlargement and a generalized increase in lung markings. He was transfused and allowed to go home. He was readmitted on December 9, 1956, quite breathless, having suffered repeated hæmoptyses and hæmatemeses. He was evidently breathless, his urine contained two-thirds albumin, there were bilateral crepitations at both lung bases, and he died rapidly in pulmonary œdema.

Pathological Findings.—The right lung weighed 1330 grammes and the left 1200 grammes; they were firm, œdematous and dark red in colour. The right kidney weighed 260 grammes and the left 250 grammes. They were pale, and their external surface was mottled with tiny dark red spots. On microscopic examination the alveolar walls are thickened and heavily infiltrated with leucocytes, and some are collapsed. Many alveoli contain red blood cells and hæmosiderin-carrying macrophages, and some contain fibrin or fluid. In some areas fibrin is disposed along the surfaces of the alveolar ducts. The glomeruli show endothelial proliferation, crescent formation and capsular adhesions and are undergoing fibrosis; some are completely hyaline. The interstitial tissue is œdematous and infiltrated with inflammatory cells.

Case VI

D.W., a fitter, aged 25 years, was admitted to hospital on February 28, 1957. For six months he had produced daily a little dirty-brown sputum. For the past two months he had been short of breath, and there had been small hard clots in the sputum in the mornings. More lately, he had suffered night sweats and constricting retrosternal pain on breathing. He had lost one stone in weight. When he was 12 years old he had been in hospital for one month following an episode of hæmaturia. His blood pressure was 140/60 mm. Hg. There were crepitations at both lung bases, and his urine contained one-sixth albumin and about 80 red blood cells per high power field. His hæmoglobin value was 5·6 grammes *per centum*, and his white cell count was 5000 per cubic millimetre with 70% of neutrophils. Bleeding and coagulation times were normal. His blood urea content was 25 milligrammes per 100 millilitres. His serum electrolytes and plasma proteins were normal. His anti-streptolysin titre was 1 : 50, and L.E. cells could not be demonstrated. No pathogens could be cultured from his sputum. The chest film showed loss of translucency in the hilar region and midzones. Although his chest film cleared temporarily, his hæmoptyses continued, and he suffered three attacks of breathlessness. Eventually, hæmaturia and œdema developed, and his blood urea level began to rise. His anæmia responded to blood transfusion, but corticosteroids did not seem to help him. He was allowed to go home on April 24, 1957. Two days later he returned, breathless and vomiting, and died very quickly.

Pthological Findings.—The right lung weighed 1540 grammes and the left 1320 grammes; they were solid and mottled and red in colour. The right kidney weighed 320 grammes and the left 290 grammes; their surfaces were smooth and pale and studded with tiny red spots. On microscopic examination the alveolar walls are thickened and sometimes appear fused. The alveoli are distended by red blood cells and hæmosiderin-carrying macrophages. There are some scattered groups of leucocytes and clumps of fibrin. The glomeruli show various degrees of cellular proliferation, inflammatory cell infiltration, crescent formation and adhesions. They appear to be undergoing fibrosis, but most are moderately cellular and only a few completely fibrosed. The interstitial tissue is œdematous and infiltrated with inflammatory cells.

Case VII

R.C., an 18-year-old fitter, was referred to hospital on August 5, 1957. Five months previously he had suffered a brisk hæmoptysis following exercise. In the previous month he had been breathless, weak and tired, and subsequently there had been repeated small hæmoptyses. He had been given cortisone and a blood transfusion by his own doctor. No urinary symptom was noted, and antibiotics had not been administered.

His family history should be recorded; five years previously an elder brother had died after hæmoptysis and bleeding from the bowel; he was said to have had renal disease as well. Eight months before a brother, aged 16 years, had coughed up some blood; his chest films were normal.

The patient's blood pressure was 125/90 mm. Hg. His urine contained two-thirds albumin and 150 red cells per high power field. His hæmoglobin value was 9·6 grammes *per centum*; his white cell count was 13,000 per cubic millimetre with 70% of neutrophils. Platelets and coagulation and prothrombin times were normal; his bone marrow showed active erythropoiesis. His blood urea content was 120 milligrammes per 100 millilitres; his serum electrolytes and serum proteins were normal. His chest film showed a progressive loss of translucency, more noticeable in the right lower lobe. The findings from bronchograms and bronchoscopy were negative, and L.E. cells could not be demonstrated. His anti-streptolysin titre was normal, and the result of a muscle biopsy was negative. In hospital he suffered from constant dirty-brown hæmoptyses and hæmaturia. A transfusion temporarily raised his hæmoglobin value. He was given cortisone in doses up to 200 milligrammes daily without apparent improvement. His blood urea content rose finally to 360 milligrammes per 100 millilitres. He became breathless during a transfusion and died suddenly almost a month after his admission to hospital.

Pathological Findings.—The right lung weighed 1170 grammes and the left 945 grammes. There were two pints of fluid in the pleural cavity. The lungs were solid and showed subpleural hæmorrhages. The right kidney weighed 160 grammes and the left 135 grammes; they were pale and speckled by tiny red areas one to two millimetres in diameter. On microscopic examination the alveolar walls have prominent lining cells and contain leucocytes and fibroblasts. The alveoli contain red blood cells, hæmosiderin-carrying macrophages, fibrin and scattered collections of leucocytes. The glomeruli show cellular proliferation, infiltration by leucocytes and extensive crescent formation. In some there is well developed fibrosis. There are inflammatory cells scattered through the interstitial tissue.

Case VIII

J.G., an 18-year-old storeman, was admitted to hospital on August 27, 1941, having sustained a sudden severe hæmoptysis. He had suffered from a cough for two years. After twelve months the sputum had become blood-stained. A chest X-ray film, at this time, showed infiltration of the right middle and lower lobes; but the patient ceased attending. Subsequently he had felt ill and short of breath and, during the two months prior to admission, had lost more than one stone in weight. The hæmoptysis recurred, but the final episode was unexpected. He was pale, breathless and anxious. His blood pressure was 160/90 mm. Hg. There was impairment of percussion note over the right lower lobe, fine crepitations throughout the right lung and a pleural friction rub over the right base. The urine contained a trace of albumin. The hæmoglobin value was five grammes *per centum*, and his white cell count was 28,000 per cubic millimetre. The patient died within five hours of admission to hospital.

Pathological Findings.—The right lung weighed 1300 grammes, the left 960 grammes. The lungs were large, heavy, solid and œdematous. The kidneys each weighed 6 ounces, and the cortex was swollen and pale and sharply demarcated from the medulla. On microscopic examination the alveolar walls show prominent lining cells and focal collections of inflammatory cells. The alveoli contain red blood cells and hæmosiderin-carrying macrophages and very little fibrin. The glomeruli show cellular proliferation, crescent formation, capsular adhesions and fibrosis. A few glomeruli are completely hyaline. There are many round cell collections in the interstitial tissue.

Case IX

M.S., a waitress, aged 22 years, was admitted to hospital on January 2, 1957. She had been dyspeptic for many years and during the past six months on some ten occasions after self-induced vomiting, there had been small amounts of blood mixed with food.

For two weeks she had had malaise, weakness and loss of weight, and, finally, a cough and severe shortness of breath had forced her to bed for a few days; but she had then returned to work.

The blood pressure was 110/70 mm. Hg. There was slight diminution of percussion note at the lung bases, diminished breath sounds and a few crepitations over the left lower lobe. The urine contained a trace of albumin. The hæmoglobin value was 4·4 grammes *per centum*; the white blood cell count was 9000 per cubic millimetre with 77% of neutrophils. Chest X-ray examination showed diffuse mottling of both middle and lower lobes; the findings from a barium meal examination were negative. She was transfused, and as her chest film cleared and her symptoms improved, she was allowed to return home on January 12. She was readmitted to hospital on February 12, complaining of upper abdominal colic relieved by vomiting. No abnormality was found on examination. The hæmoglobin value was 5·9 grammes *per centum*, and the blood urea content was 230 milligrammes per 100 millilitres.

Pathogens were not cultivated from her sputum. She ran an intermittent temperature up to 101° F. and did not respond to protein-free parenteral feeding. Her blood urea content rose to 300 milligrammes per 100 millilitres, she developed basal crepitations and breathlessness, and she died on February 21, 1957.

Pathological Findings.—The lungs were hæmorrhagic and œdematous; the kidneys were pale and swollen. On microscopic examination the alveolar walls show prominent lining cells and focal collections of leucocytes; some have broken down and are represented by buds. The alveoli mostly contain red blood cells and a few hæmosiderin-carrying macrophages. Many glomeruli show extensive endothelial proliferation, crescent formation and various degrees of fibrosis. Some contain clumps of amorphous bright eosinophilic material, suggesting recent severe damage. Interstitial tissue shows moderately severe periglomerular inflammation and inflammatory cell infiltration. Some arterioles show patchy intimal thickening.

CLINICAL FEATURES

These nine patients comprise six patients admitted to the Royal Melbourne Hospital between 1955 and 1957, one admitted to the Alfred Hospital in 1957, and two other patients

their boundaries outlined by intraalveolar leucocyte collections. The alveolar contents are red cells, hæmosiderin-carrying macrophages and scattered polymorphonuclear leucocytes. The alveolar ducts are dilated and contain fibrin, red cells and leucocytes. The glomeruli show endothelial proliferation and prominent basement membranes. Some tufts are adherent to their capsules; in others, tiny crescents are beginning to form. The interstitial tissue of the heart is œdematous and contains a few round cells.

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Case IX

M.S., a waitress, aged 22 years, was admitted to hospital on January 2, 1957. She had been dyspeptic for many years and during the past six months on some ten occasions after self-induced vomiting, there had been small amounts of blood mixed with food.

For two weeks she had had malaise, weakness and loss of weight, and, finally, a cough and severe shortness of breath had forced her to bed for a few days; but she had then returned to work.

The blood pressure was 110/70 mm. Hg. There was slight diminution of percussion note at the lung bases, diminished breath sounds and a few crepitations over the left lower lobe. The urine contained a trace of albumin. The hæmoglobin value was 4·4 grammes *per centum*; the white blood cell count was 9000 per cubic millimetre with 77% of neutrophils. Chest X-ray examination showed diffuse mottling of both middle and lower lobes; the findings from a barium meal examination were negative. She was transfused, and as her chest film cleared and her symptoms improved, she was allowed to return home on January 12. She was readmitted to hospital on February 12, complaining of upper abdominal colic relieved by vomiting. No abnormality was found on examination. The hæmoglobin value was 5·9 grammes *per centum*, and the blood urea content was 230 milligrammes per 100 millilitres.

Pathogens were not cultivated from her sputum. She ran an intermittent temperature up to 101° F. and did not respond to protein-free parenteral feeding. Her blood urea content rose to 300 milligrammes per 100 millilitres, she developed basal crepitations and breathlessness, and she died on February 21, 1957.

Pathological Findings.—The lungs were hæmorrhagic and œdematous; the kidneys were pale and swollen. On microscopic examination the alveolar walls show prominent lining cells and focal collections of leucocytes; some have broken down and are represented by buds. The alveoli mostly contain red blood cells and a few hæmosiderin-carrying macrophages. Many glomeruli show extensive endothelial proliferation, crescent formation and various degrees of fibrosis. Some contain clumps of amorphous bright eosinophilic material, suggesting recent severe damage. Interstitial tissue shows moderately severe periglomerular inflammation and inflammatory cell infiltration. Some arterioles show patchy intimal thickening.

CLINICAL FEATURES

These nine patients comprise six patients admitted to the Royal Melbourne Hospital between 1955 and 1957, one admitted to the Alfred Hospital in 1957, and two other patients

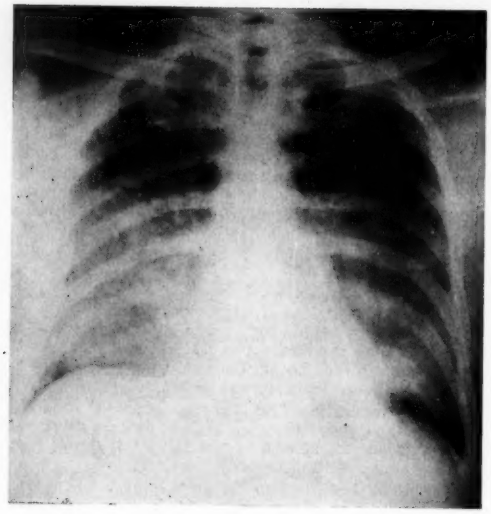

FIGURE I

Case I. X-ray photograph of the chest, showing coarse mottling in both lungs, more pronounced at the hila

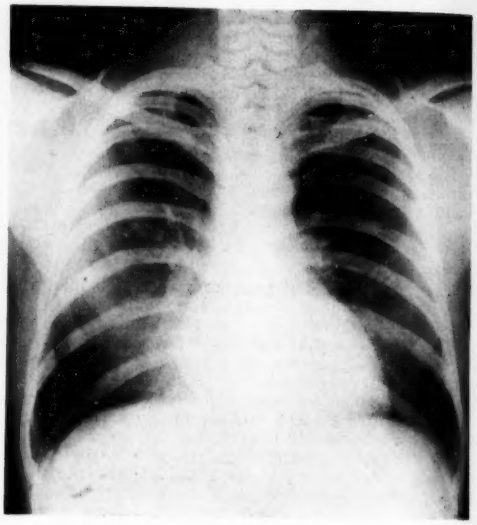

FIGURE II

Case VII. X-ray photograph of the chest, showing loss of translucency, more noticeable on the right side

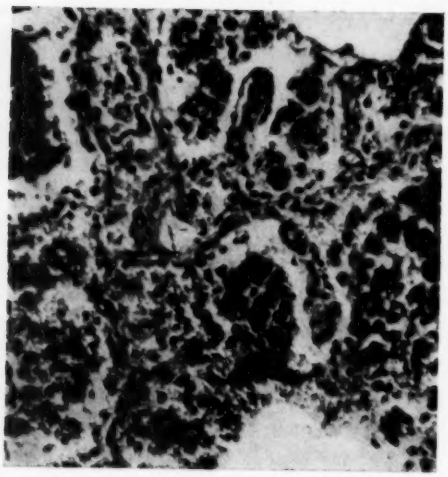

FIGURE III

Case III. Photomicrograph of the lung, showing thickened and retracted alveolar walls. The alveoli contain macrophages and red cells. Hæmatoxylin and eosin. (×100)

FIGURE IV

Case IX. Photomicrograph of the lung, showing masses of red blood cells and a few macrophages within alveoli. Hæmatoxylin and eosin. (×125)

whose histories were found in a search of the records of the Royal Melbourne Hospital. Seven of the patients were young adults around 20 years of age, and two were in their forties. Seven were males (including both patients in their forties), and two were females.

Presenting Symptoms

Eight patients presented with hæmoptysis. In six patients it was the initial symptom, in one (I.W.) it occurred late in the course of a respiratory infection, with muco-purulent sputum and in another (E.H.) it developed a few days after the onset of swelling of her face and ankles. The other patient (M.S.) presented with cough and shortness of breath, but for some months had brought up small quantities of blood mixed with food. In four of these patients, the existence of a renal lesion was at first overlooked.

Duration

In four patients (J.S., I.W., H.K., and E.H.) the duration of the illness was about two weeks; in four (A.M., D.W., R.C., and J.G.) it was three, eight, five and twelve months respectively, and in the last patient (M.S.) it was apparently nine weeks, though it may possibly have been much longer.

Symptoms

Hæmoptysis was the commonest as well as the presenting symptom. It was generally not profuse, but rather persistent, and occasionally was more troublesome in the morning. Usually the blood was bright red, sticky and homogeneous, although at the onset it might be brown or mixed with mucus or mucopus. At first there was at the most no more than mild breathlessness, so that the patient continued at his work. Severe breathlessness, comparable with that of pulmonary œdema, was a terminal event and often an unexpected one. Nearly all the patients complained of increasing weakness and tiredness, and more than half of nausea and vomiting. Three patients vomited either small or large quantities of blood, and this obscured the diagnosis. Two patients suffered night sweats, and three of those whose illness was more protracted lost up to a stone in weight.

Physical Findings

The outstanding sign was pallor, the patient's hæmoglobin values ranging from 4·4 to 9·6 grammes *per centum*. None was hypertensive, and only four (J.S., I.W., E.H. and J.G.) appeared dyspnœic. In these four patients bilateral crepitations were heard on auscultation, and none survived longer than three days.

One other patient (D.W.) had basal crepitations and one patient (J.S.) an epididymitis. All except one (H.K.) showed hæmaturia or albuminuria, though in two (J.G., M.S.) there was no more than a trace. No other abnormal physical sign was elicited.

Investigations

There was usually a pronounced neutrophil leucocytosis, especially in the acute stages of the illness. In only one patient (D.W.) was there a leucopenia. The blood urea content was estimated in five patients (I.W., A.M., D.W., R.C. and M.S.), the levels being 60, 270, 25, 120 and 230 milligrammes per 100 millilitres, respectively. In the first patient the illness was of two weeks' duration and in the others of some months' duration when the estimation was made.

Smears and cultures of the sputum yielded a mixed and non-pathogenic flora. In one patient (J.S.) a coagulase-positive staphylococcus was cultured from a throat swab, but not from the sputum, nor from the lung at autopsy. X-ray examination of the chest showed either bilateral loss of translucency or fine to coarse mottling, the change being much more obvious in the hilar region (Figure I) and least at the apices. These appearances are, of course, by no means specific. In the early stages of the illness the loss of translucency may be so slight that its significance may be appreciated only in retrospect. Two patients at first showed unilateral changes (Figure II), and this occurred also in one of the cases previously reported (Clinico-Pathological Conference No. 21, 1954). In the patients who survived for some weeks after admission, a large variety of tests, including studies on blood coagulation, was carried out with uniformly negative results.

PATHOLOGICAL FEATURES

The Lungs

Macroscopically, the lungs were bulky and heavy, averaging about 1100 grammes in weight, either dark red in colour or showing a mosaic pattern of red and pink. They felt solid and moderately firm, even after fluid was expressed, as it frequently could be.

Microscopically the alveolar walls are thickened, with smooth lining cells and infiltrated by polymorphonuclear leucocytes. Their capillaries are patent and contain red blood cells. The alveoli are filled with red blood cells, pigment-carrying macrophages (Figures III and IV), fibrin and a few polymorphonuclear leuco-

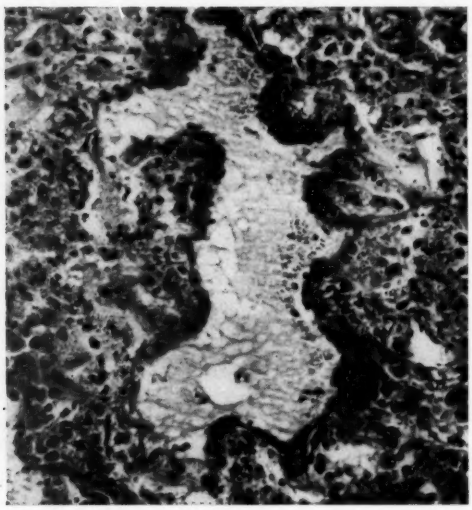

FIGURE V

Case IV. Photomicrograph of the lung, showing a dilated alveolar duct lined by a hyaline membrane. The surrounding alveoli contain red cells, macrophages and fibrin. Hæmatoxylin and eosin. (×100)

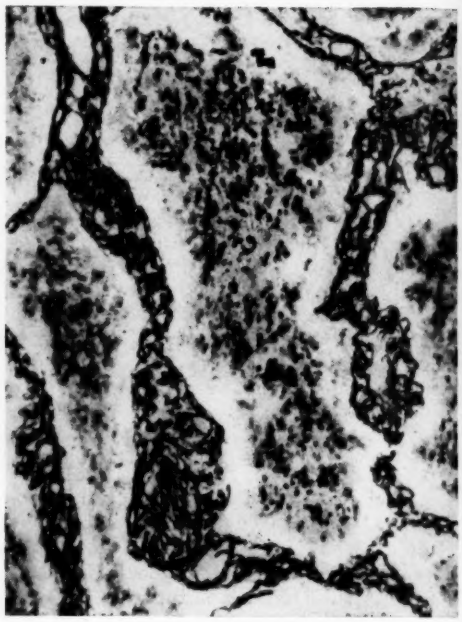

FIGURE VI

Case II. Photomicrograph of the lung, showing approximation of collapsed alveolar walls. Reticulin stain. (×125)

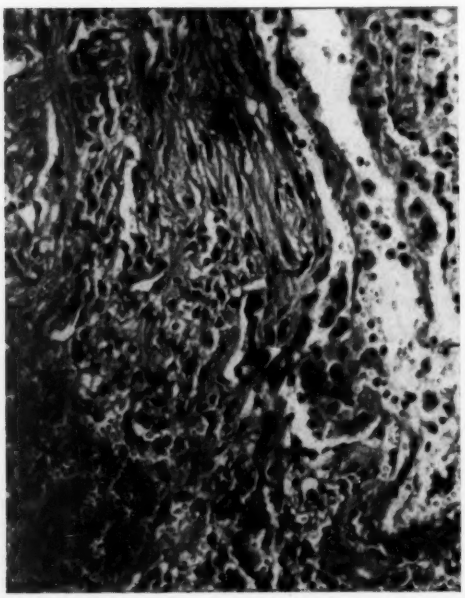

FIGURE VII

Case I. Photomicrograph of the lung, showing newly-formed fibrous tissue along one side of an alveolar duct. Hæmatoxylin and eosin. (×125)

FIGURE VIII

Case II. Photomicrograph of the lung, showing fibrous tissue along the wall of an alveolar duct. Reticulin stain. (×100)

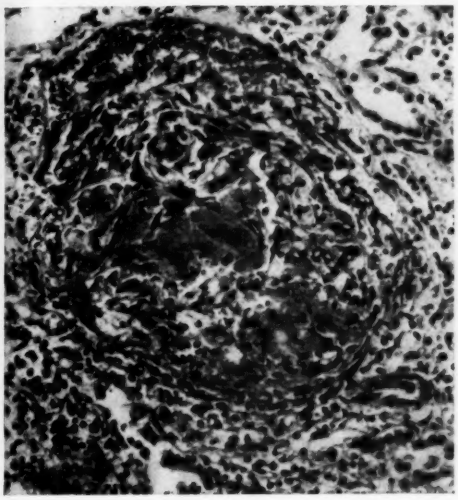

FIGURE IX

Case II. Photomicrograph of a glomerulus, showing cellular proliferation, structureless eosinophilic material and inflammatory cell infiltration of the tuft and surrounding tissue. Hæmatoxylin and eosin. (×125)

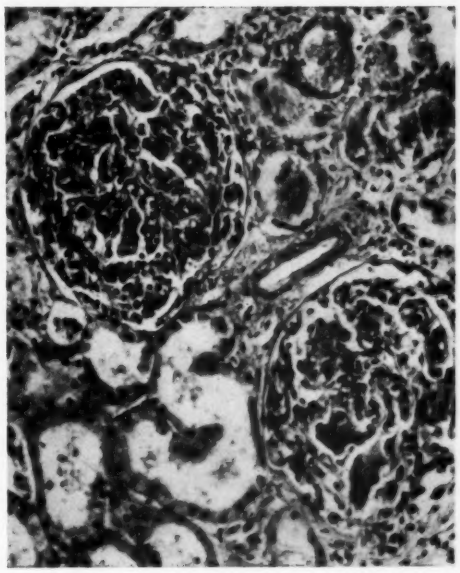

FIGURE X

Case II. Photomicrograph of the kidney, showing giant cells in a damaged glomerulus. Hæmatoxylin and eosin. (×100)

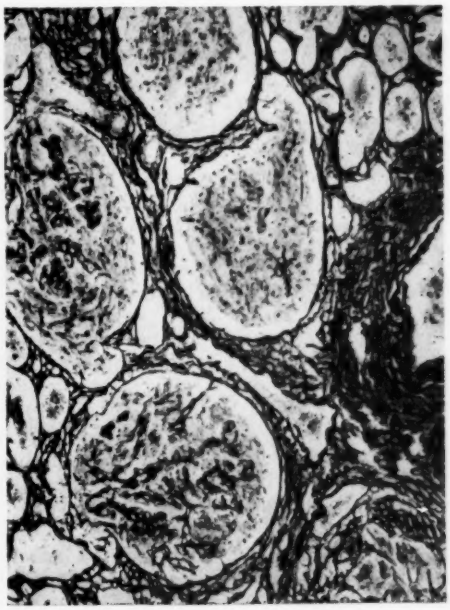

FIGURE XI

Case II. Photomicrograph of the kidney, showing disintegration of the framework of the glomerular tufts and condensation of the supporting tissue between the glomeruli. Reticulin stain. (×100)

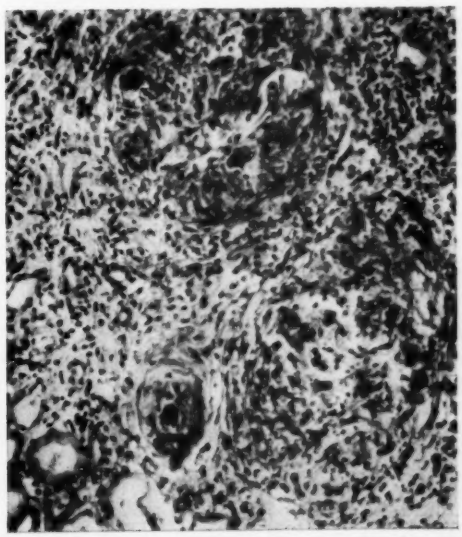

FIGURE XII

Case I. Photomicrograph of the kidney, showing severely damaged glomeruli and an artery with swollen eosinophilic walls. Hæmatoxylin and eosin. (×100)

cytes; a small minority contain either air or fluid. Red blood cells and macrophages are the most striking and consistent of these intra-alveolar collections.

In four patients (J.S., H.K., A.M. and E.H.) hyaline membranes line alveoli and alveolar ducts (Figure V). Some bronchioles are filled with red blood cells, but inflammatory changes are not apparent. The vessels are normal. In all patients some alveolar walls have broken down and are represented by rounded stumps (Figure III). In four patients (J.S., I.W., H.K. and M.S.) this is a prominent feature. Sometimes the alveolar walls are indistinct and outlined by intraalveolar polymorphonuclear leucocyte collections. Necrotizing alveolar lesions (Parkin *et alii*, 1955) are not seen, but in one patient (M.S.) there are focal collections of polymorphonuclear leucocytes in the alveolar walls.

Some alveoli have collapsed, and the outlines of their walls are difficult to make out (Figure VI). In two patients (J.S. and I.W.) there are small areas of fibroblastic proliferation replacing and distorting alveoli (Figures VII and VIII).

In one patient (E.H.) hæmorrhage and pigment-carrying macrophages represent only a small proportion of the alveolar contents, and here the red cell outlines are irregular, and there are pigment granules around them, suggesting that they may have been present longer than the other changes in the lung. In this patient fluid and fibrin form a considerable portion of the alveolar contents. Similar appearances suggest that much of the hæmorrhage in another patient (A.M.) is of some duration. In contrast, in a third patient (M.S.), there is an abundance of apparently freshly shed red cells, these retaining their normal shape and staining characteristics and very few macrophages (Figure IV).

The Kidneys

The kidneys were large and pale, and approximating 200 grammes in weight, with a smooth surface and a wide, well-demarcated cortex. In some specimens, the surface and substance of the cortex were speckled with tiny red spots.

The microscopic appearances fall into two groups and in each case correspond roughly with the duration of the patient's illness. In all patients, every glomerulus is damaged.

In the first group of subjects (J.S., I.W., H.K. and E.H.) the inflammatory process is more acute. The glomerular tufts show swelling, endothelial proliferation and polymorphonuclear leucocyte infiltration, and the capsular spaces are usually still present.

There is relatively little tubular damage, and the tubules may contain red cells or casts.

In two of the subjects (J.S. and I.W.) the changes are much more severe and possibly of longer duration. There are deposits of structureless eosinophilic material in the glomeruli (to a much greater extent in the first patient) and occasional giant cells and well-developed crescent formation (Figure X). Around the glomeruli is a zone of condensed supporting tissue containing damaged tubules, inflammatory cells and a few fibroblasts. These changes indicate severe glomerular damage

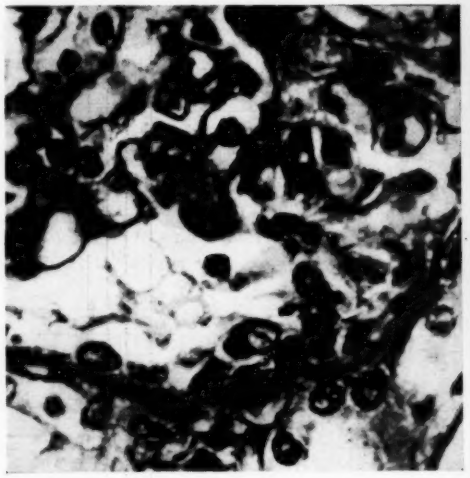

FIGURE XIII

Case III. Photomicrograph of portion of a glomerulus showing early crescent formation. Hæmatoxylin and eosin. · (×500)

(Figure X). Occasional arterioles show intimal thickening, and in the first patient (J.S.) the walls of the small artery stain deep pink with eosin (Figure XII), are swollen and have lost their structural definition, and a few glomeruli are completely fibrosed.

In two subjects (H.K. and E.H.) the glomerular changes are less severe, and of all those seen in this series these alone seem potentially reversible.

Crescent formation is early or minimal (Figure XIII), and the changes in the tubules and interstitial tissue, if present, are focal and less extensive. The vessels are normal.

The second group of subjects (A.M., D.W., R.C. and J.G.) is distinguished by extensive

crescent formation, obliteration of the capsular spaces and partial or complete fibrosis of some tufts. In three cases (A.M., D.W. and J.G.) there is patchy round-cell infiltration, and the interstitial tissue is œdematous.

In the remaining subject (R.C.) there is, in addition, a pericapsular fibrosis and polymorphonuclear leucocyte infiltration of the interstitial tissue, especially around the glomeruli (Figure XIV), In all cases many tubules are dilated and contain red cells, white cells and casts. The vessels are normal.

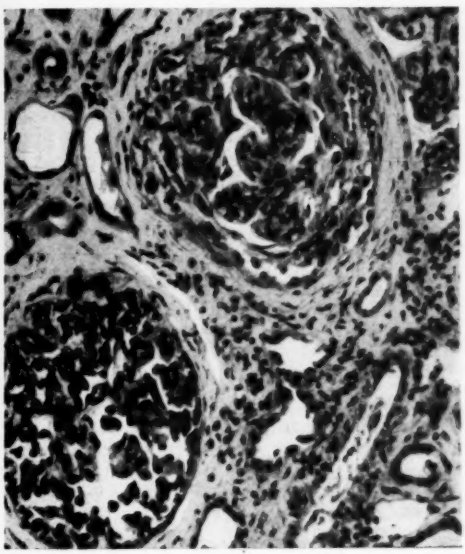

FIGURE XIV

Case VII. Photomicrograph of the kidney. The glomeruli show cellular proliferation and pericapsular fibrosis. There is inflammatory cell infiltration of the interstitial tissue. Hæmatoxylin and eosin. (×125)

In the last subject (M.S.) the glomerular changes have the characteristics of both groups. The glomeruli show proliferation, crescent formation and capsular fibrosis, and a few exhibit partial or complete hyaline change. Others show, in addition, foci of eosinophilic structureless material and polymorphonuclear leucocyte infiltration of the tuft and periglomerular interstitial tissue. There is also some inconspicuous hyaline intimal thickening of the arterioles.

There was, with two exceptions which are set out in the case reports, no demonstrable lesion, and, in particular, there was no arterial change in any other organ.

DIAGNOSIS

This syndrome should be suspected when no local cause for an hæmoptysis can be demonstrated. Although the X-ray changes are not themselves specific, these suspicions should be increased if the chest films show bilateral diffuse mottling or loss of translucency.

The most acute cases of this syndrome may be clinically indistinguishable from cases of glomerulonephritis complicated by severe bronchopneumonia. Two such cases were encountered : one in the patient M.C., a 25-year-old Maltese labourer, the other in an 8-year-old boy, B.D. Both exhibited severe breathlessness, cyanosis and scanty hæmoptysis, clinical and X-ray evidence of a diffuse bilateral pulmonary lesion, signs of a mild glomerulonephritis and a neutrophil leucocytosis. No pathogens could be grown from the sputum. Both patients died soon after admission to hospital. On microscopic examination of the lungs some alveoli were found to be filled with red cells and œdema fluid, but many more with polymorphonuclear leucocytes.

Hæmoptysis may occur, upon rare occasions, late in the course of progressive glomerulonephritis with renal failure. Especially when there is bleeding from other sites, an increased capillary permeability sometimes associated with a high blood urea content may then be an important factor in its development. Owing to the symptom sequence this diagnosis is easily made.

Even when the onset of the condition is insidious and its course prolonged, hæmoptysis may not at first be accompanied by evidence of a renal lesion. Although hæmoptysis is an extremely uncommon manifestation of a clotting defect, studies on blood coagulation should be carried out, as well as bronchoscopy and bronchography, in an attempt to exclude a local lesion.

Early in the course of the condition, renal lesions may not be far advanced, so that renal function tests will be of no great value. Consequently, if no cause for the bleeding can be found, and this syndrome is suspected, it may be advisable to consider performing renal biopsy.

TREATMENT

Because of the difficulties in diagnosing the more acute examples of this condition it is necessary, in these, to use antibiotics in massive doses. Corticosteroids were employed in two of our cases without benefit. They have also been found wanting in the management of severe rheumatic pneumonia (Lustok and

Kuzma, 1956) and for probably the same reason—that is to say, the lesions were far too extensive. With prompt and early diagnosis the results may be much better. Blood transfusions are often necessary to correct the severe anæmia; because of the danger of pulmonary œdema, they should be small, probably no more than 500 millilitres per day, or, better, the packed cell content.

PROGNOSIS

In all the cases reported so far the patients have died—some within three weeks; others have survived as long as twelve months. Of the nine patients in this study, all died from pulmonary hæmorrhage and œdema, but two were anuric, a third was probably so, and three other patients were in a state of renal failure. In these six patients and in a seventh (J.G.) the glomeruli appeared to be irreversibly damaged. In the remaining two patients (E.H. and H.K., the glomerular lesions were mild or minimal, and the patients might have recovered had they survived the acute pulmonary episode. The initial general symptoms incommode the patients so little and the signs are so trivial that in mild cases the patients may well survive with the condition undiagnosed.

DISCUSSION

The clinical and pathological picture built up from an experience of these nine patients supplements that already described in the literature. The initial manifestation is usually a small hæmoptysis, and this recurs as the disease progresses, to end fatally either within two to three weeks or after some months. In one patient an unexplained hæmoptysis, twelve months before his final illness, and small recurrent hæmatemeses for many months in another, suggest that the duration of the disease may not always be so short as it seems in other cases. In both of these patients some glomeruli were completely fibrosed. Quite often, a renal lesion is not at first detected, and in one patient the glomerular changes were minimal. The converse was observed in another patient, who was not included in this series because scant autopsy material was available. This was a 39-year-old housewife, with hæmaturia of eight months' duration, who had for two months been breathless and had noticed a fleeting skin rash and pain in her joints and for two or three weeks had suffered an occasional hæmoptysis. Her blood urea content was 80 milligrammes per 100 millilitres, and she died within a week of admission to hospital. She was found to have recent pulmonary hæmorrhage and a subacute glomerulonephritis, with proliferation of the tufts and capsules.

The hæmoptyses are recurrent and at first not accompanied by breathlessness, consistent with a focal rather than a diffuse process—a pattern observed also in rheumatic pneumonia (Rich and Gregory, 1943).

In time the lesions become confluent, and breathlessness and pulmonary œdema complete the clinical course. Even at this stage the pulmonary lesions may resolve, but they recur before the end of the illness. As in rheumatic pneumonia, a relatively high proportion of the lung needs to be involved before symptoms appear (Naish, 1928).

Two factors may influence the course of the lesions in the lung. One is the rising blood urea content and the other is continued activity, for, with one exception, all these patients remained at work after their first symptoms. Both of these factors may further modify pulmonary capillary permeability and increase losses of cells and protein into the alveoli.

Although there is no relation between the severity of the lesions in lung and kidneys, it has so far been assumed that they are both effects of the same disease process. At present there seems no ground for disputing this.

When the syndrome was first described, Goodpasture (1919) felt that it was an unusual manifestation of influenza; the findings in the lungs in these cases, however, are not those of a severe hæmorrhagic bronchopneumonia. In such cases, the pneumonia is nearly always due to secondary staphylococcal infection and the severe damage to its exotoxins (Hers, 1955); hence one would expect extensive destruction of bronchial and bronchiolar epithelium and, throughout the lung, collections of polymorphonuclear leucocytes and staphylococci.

It must be evident from the histories of these patients that uræmia plays no part in the initiation of the lesions in the lungs. Before death, however, they must often be modified by the renal dysfunction evidenced by a very high blood urea content. Although not specific, the radiological appearances of the lung in uræmia resemble those in this syndrome (Doniach, 1947), and both the macroscopic and microscopic appearances have a number of features in common, but are readily distinguished by the severity of the intraalveolar hæmorrhage in this syndrome, which is either absent in uræmia or, if present, is of a minor degree (Doniach, 1947; Hopps and Wissler, 1955). Necrosis of alveolar walls with associated polymorphonuclear leucocyte collections was

considered to represent an important difference between the pulmonary lesions of this syndrome and those sometimes accompanying uræmia (Parkin *et alii*, 1955). Such lesions were not present in these patients, though there were many collections of leucocytes in or very close to the alveolar walls. The lesion is probably an index of the severity of the causal process rather than a guide as to its nature.

The pulmonary lesions bear a closer resemblance to those occurring in rheumatic fever (Hadfield, 1938). In all except one of these cases, the intraalveolar hæmorrhage is much more prominent than in rheumatic pneumonitis. Similar pulmonary lesions have been demonstrated in sulphonamide sensitivity (French, 1946), and still others have been produced experimentally in rabbits sensitized to egg white protein (Cannon *et alii*, 1941). However, in this syndrome, there is no evidence of allergy or drug sensitivity, nor of implication of any drug used in treatment.

Renal and pulmonary lesions have been described in *polyarteritis nodosa*. In an analysis of 14 patients, Davson *et alii* (1948) differentiated a group characterized clinically by chest symptoms, leucocytosis and albuminuria. The patients were normotensive, and four became uræmic. The pulmonary changes included infarction and small pale foci resembling miliary tubercles and microscopic evidence of arterial lesions. The characteristic renal lesions were a patchy fibrinoid necrosis of glomerular tufts, crescent formation, partial fibrosis of glomeruli and periglomerular collections of round cells and leucocytes. One patient suffered recurrent hæmoptyses, but the lung changes were those of polyarteritis. Similar glomerular lesions have been described in patients dying of uræmia (Wainwright and Davson, 1950) and in patients with Bright's disease observed at the London Hospital (Russell, 1929; Ellis, 1942) and should arouse suspicion of polyarteritis. However, arterial lesions are not always to be found, and this type of glomerular lesion may indicate the severity of the process producing it rather than its nature.

In a more recent analysis of 104 patients with *polyarteritis nodosa* (Rose and Spencer, 1957), those with lung involvement showed nasal or middle ear granulomata, eosinophilia, pulmonary arterial lesions, and necrotizing and granulomatous lesions both in the lungs and in other organs. This association of lesions has been recognized previously (Wegener, 1939), and the necrotizing glomerular lesions (Wegener, 1939; Fahey *et alii*, 1954) are similar to those described by Davson *et alii* (1948) and to some of those seen in certain of the patients reported here.

Acute arterial lesions, necrosis and perivascular inflammatory cell infiltration were present in the spleen in Goodpasture's original patient, in the patient from Hammersmith Hospital and in four of the seven patients described by Parkin and his colleagues. The last eight patients all showed severe glomerular lesions comparable to those described by Davson *et alii*. In one patient (Clinico-Pathological Conference No. 21, 1954) there was a small pulmonary infarct, but with one other exception (Parkin *et alii*, 1955) arterial lesions have not been found in the lungs in this syndrome. In the present series there was only one example of a renal arterial lesion, and only three patients showed necrotizing glomerulonephritis and arteriolar changes. Indeed, two patients showed only early or minimal glomerular lesions.

Pulmonary involvement in *polyarteritis nodosa* appears to have its own clinical and pathological pattern. Any relation between the two conditions rests chiefly upon the similarity of certain of the glomerular lesions, and this may be no more than an expression of the severity of the causal lesion. The pathological lesions in this syndrome are not themselves specific and in consequence provide little information about their underlying mechanism. They neither help to differentiate the syndrome from a number of related conditions nor explain its essential feature, the combination of pulmonary and glomerular capillary damage.

ACKNOWLEDGEMENTS

Our thanks are due to the honorary medical staff of the Royal Melbourne Hospital for access to the hospital records and permission to study their patients. One patient (M.S.) was admitted to the Alfred Hospital under the care of Dr. T. E. Lowe, and we are indebted to him for his courtesy in allowing us to include her history in this series. For permission to study one patient (B.D.) mentioned in the discussion, we wish to thank the Medical Superintendent of the Footscray Hospital.

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DIABETIC MORTALITY IN AUSTRALIA[1]

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SUMMARY

Of 3140 patients (1040 males and 2100 females) admitted to the clinic (Royal Prince Alfred Hospital, Sydney) between 1932 and 1947, 894 have died. Coma was the cause of death in 43, of whom 11 were under the age of 25 years. The major cause of death was arterial degeneration (131 males and 308 females). Gangrene (48), cancer of the pancreas (15) and other causes (74) were important causes of death. Cancer of the pancreas and, to a lesser extent, cancers of the female genital organs were significantly more common in the diabetics than in the general population.

The series was used to study the age of onset and the sex incidence of diabetes. Mortality rates were computed for each age group. Mortality was particularly heavy at ages under 25 and over 55 years.

The death certificates showed that the official statistics assign only a small proportion of the deaths of diabetics to the title "Diabetes". In 60% of the 894 clinic patients dying, diabetes was not counted by the statistician as a cause of death.

IN a survey of the fate of the patients of the Diabetic Clinic at the Royal Prince Alfred Hospital, Sydney, all patients entering the clinic from 1932 onwards were included except (*a*) those having a country address and making only a few visits, (*b*) those who made only one visit and (*c*) those who had attended the clinic for consultation only. The remainder were followed up to the end of 1947. This experience has been divided into two parts: (i) 1932 to 1940, and (ii) 1941 to 1947. It was realized, as a result of this study, that many of the patients had not been attending the clinic regularly, and some had transferred to other clinics. In the absence of a formal notification from the patient, he was still counted as a member of the clinic until his death or the end of 1947.

For the years, 1948 to 1952, it was decided to count only those patients who had attended the clinic in 1947 or at a later date; the rule was that anyone attending in 1947 would be counted as a patient from the beginning of 1948 unless death or transfer to another clinic had occurred before January 1, 1948; other clinic patients not reporting in 1947 were to be counted as new admissions at the time of their first visit since the beginning of 1948. It was hoped that the follow-up would be completed in 1953, but over 500 of the patients had not attended the clinic during 1953. A carefully worded stamped and addressed letter card was sent to each, with a covering note. About 60% responded, or their relatives made a note that they had died.

For all patients whose condition at the end of the period was not known to us, we first inquired whether they had been admitted to the Royal Prince Alfred Hospital as in-patients. We next visited other city clinics to find any patients transferred from our clinic. Then we consulted the electoral rolls. Finally, if we had any information that the patient had died, we obtained permission to look for a copy of their death certificate in the office of the Registrar-General. Since our aim was limited, we have noted only the fact of the patient's being alive or dead at the end of the survey time.

THE PATIENTS

The total numbers of patients entering the clinic before 1947 were 835 males and 1711 females. Since 1947, 205 males and 389 females have entered the survey. We may discuss the age and sex incidence in those patients entering the clinic before 1947.

Sex.—Table I shows that 749, or 32%, were males and 1582, or 68%, females. The sex distribution varies with age of onset. Up to the

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age of 35 years, the males and females are approximately equal in number—172 males to 193 females; but in the age group 35 to 39 years, we have 41 males to 94 females, and in every other high age there are more than twice as many females as males.

Age at Onset of Diabetes.—The percentages of males or females with a recorded age of onset of the disease are given in Table I. We have compared our figures with those of the George F. Baker Clinic in Boston (Joslin *et alii*, 1952).

TABLE I

The Age Distribution of the Onset of Diabetes

Age (Years)	Patients Admitted to Diabetic Clinic at Royal Prince Alfred Hospital Sydney, 1932 to 1947		Patients at George F. Baker Clinic (Joslin, 1952) in the Years 1939 to 1947	
	Males	Females	Males	Females
0 to 9	2·3	0·8	4·9	4·6
10 to 14	1·9	2·4	5·0	5·2
15	2·7	1·8	3·7	3·3
20	5·3	2·3	3·5	3·2
25	4·7	1·9	4·8	2·9
30	6·1	3·0	6·9	4·1
35	5·5	5·9	8·1	5·9
40	10·5	9·7	11·4	8·0
45	9·2	12·4	12·9	11·8
50	13·6	16·6	13·0	14·0
55	12·3	16·1	10·4	13·6
60	12·3	13·2	7·1	10·8
65	7·1	8·7	4·1	6·7
70	4·1	3·4	2·4	2·9
75	1·6	1·2	1·4	1·4
80 and over ..	0·8	0·5	0·4	0·7
Total	100·0	100·0	100·0	100·0
Number ..	749	1582	2420	2909

Similar figures are given by Harris (1949), and a number of surveys are cited by Harris and McArthur (1951) which present findings similar to our own. Our patients tend to be slightly older at onset than Joslin's, but some of this difference is possibly due to differing hospital policies, particularly as regards children, since children under 14 years of age have tended to be admitted to the Royal Alexandra Hospital for Children rather than to the Royal Prince Alfred Hospital. We may note that the age of onset is quite definite in children, whereas in adult life the onset may be gradual and the disease diagnosed only in the course of a routine examination.

Joslin *et alii* (1952) comment that fresh diabetes becomes increasingly uncommon with advancing age. This is borne out by our figures. If we assume that the population served by our hospital had the same age distribution as the Australian population for the same years, then the rate of onset is greatest in our series at ages 60 to 64 years, and then declines as old age is reached. Owing to the age structure of the

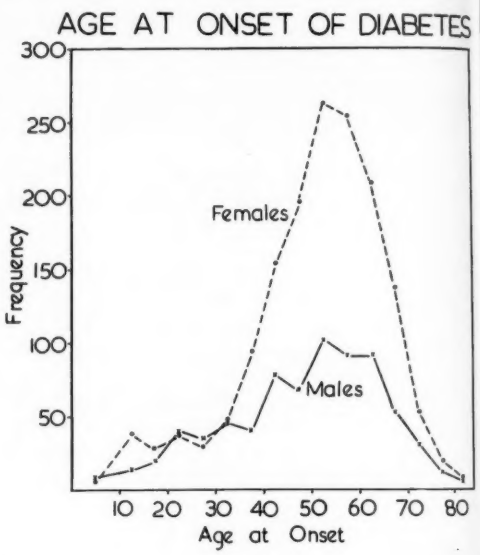

FIGURE I

The age distribution of onset of diabetes in patients entering the Royal Prince Alfred Hospital Diabetic Clinic in the years 1932 to 1947

population, the onset is most commonly observed at ages 50 to 54 years in both sexes. The ages of Bell's (1952) patients tend to be somewhat older than either ours or Joslin's, and this seems to be explained by his being an autopsy series.

TABLE II

The Years of Life Experienced by Patients in the Clinic (Royal Prince Alfred Hospital)

Ages (Years)	Years of Life Experienced in the Period[1]					
	1932 to 1940		1941 to 1947		1948 to 1952	
Under 15 ..	10·5	23·5	25·5	16	31·5	39·5
15 to 24 ..	86	139	112	221·5	49·5	97·5
25 to 34 ..	177	90·5	245	252	82	149
35 to 44 ..	178	247·5	388	372	113·5	164
45 to 54 ..	274	613·5	556·5	1146	179·5	374
55 to 64 ..	239	794	656	1884	350·5	850·5
65 to 74 ..	198·5	445	396·5	1396	254	750·5
75 and over ..	51	44·5	185·5	312·5	91	189·5
Total ..	1214	2397·5	2565	5600	1151·5	2614·5

[1] A patient already in the clinic at the beginning who completes the year experiences one year; if he dies or transfers to another clinic during the year, he is said to experience half a year. If he joins the clinic during the year and completes it, he is said to experience half a year. If he enters and leaves the clinic in the same year, he is said to have experienced 0 year.

Years of Life Experienced.—In Table II are given the years of life experienced in the clinic. The years of life in 1948 to 1952, a period of five years, are much fewer than the years of life experienced in 1941 to 1947, a period of seven years, chiefly because of the different definition of clinic patient. The actual numbers attending the clinic were still increasing in the later period.

THE MORTALITY OF CLINIC PATIENTS

The total deaths for the clinic patients for the twenty years 1932 to 1952 were 894. In Table III and Figure II are given the mortality rates defined in a customary manner, deaths per 1000 years of life experienced in each age group. For any of the three periods, the mortality is high in the elderly patients and also in the children. At ages 15 to 24 years, the death rate is less in females. There is a tendency for this to be so at other ages.

TABLE III

The Death Rates of Clinic Diabetic Patients (Royal Prince Alfred Hospital)

Age (Years)	Deaths per Thousand per Annum in the Years					
	1932 to 1940		1941 to 1947		1948 to 1952	
	Males	Females	Males	Females	Males	Females
15 to 24	116	43	36	9	19	0
25 to 34	28	44	12	24	12	0
35 to 44	39	48	23	40	9	18
45 to 54	55	57	52	36	28	24
55 to 64	105	60	78	57	49	29
65 to 74	116	124	91	67	87	85
75 and over	118	315	108	109	99	95

CAUSES OF DEATH

In 17 cases out of 894 we were unable to find the record of death in either hospital or Registrar-General's report. This may be explained by the patient's not dying within the State of New South Wales, or perhaps more frequently, his death being registered under a different name. We may consider the death's of the 300 males and 594 females in broad classes of interest shown in Tables IVA and IVB.

Diabetes.—Diabetes (unqualified) was given as the cause of death for 26 males and 35 females. As these appear to occur at younger ages than the general run of the deaths, it is possible that a number of them are deaths in coma.

Coma.—There were certified 22 deaths of males and 21 deaths of females due to coma. Of these, seven males and four females were under 24 years of age, the total deaths in that age group being 26. However, only one death in coma was certified after 1947. Coma was a very grave complication in diabetics in the early years of our clinic. Thus Millard (1934) reported the deaths of 16 of 30 patients admitted in coma to the Coast Hospital, Sydney. In his series, 12 out of 34 patients with gangrene died.

Gangrene.—In seven males and 24 females, death was due to gangrene. Some further deaths from this cause are perhaps included in the group of purulent infections. These deaths seem to be distributed between the sexes in approximately the same ratio as the years of life experience (Table I). More than half of the deaths have occurred above the age of 65 years. This is in agreement with other observers (e.g., Bell, 1931).

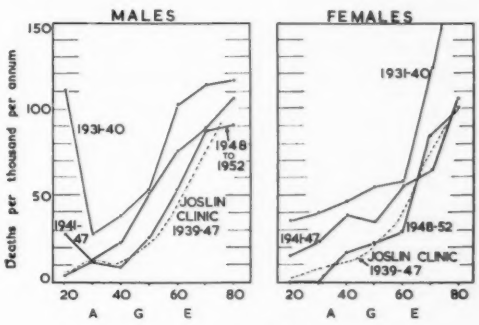

FIGURE II

The mortality rates of clinic patients in the Royal Prince Alfred Diabetic Clinic compared with those of Joslin

Arterial Degenerations.—We have included among arterial degenerations the cerebral catastrophes, coronary occlusion, atheroma, arteriosclerosis and hypertension. These are the chief causes of death, accounting for 131 males and 308 females.

Tuberculosis.—In 27 males and 21 females death was due to tuberculosis. It is an especially important cause in the young. Root and Dickson (1952) emphasize the importance of tuberculosis and point out that in the past tuberculosis has been usually quite advanced before diagnosis. They practise, as we do, annual X-ray examinations on their clinic patients.

Hæmochromatosis.—There were five male patients and two female patients certified as dying with hæmochromatosis. This is in keeping with the view that it is relatively uncommon in women. Maddox and Durie (1934) pointed out

that perhaps it was more common in women than is usually thought.

Gall-Bladder Disease.—No male patients and five female patients were certified as dying with gall-bladder disease, which may be much less common than was formerly believed.

Purulent and Acute Infective Diseases.—These infections caused 17 deaths in males and 32 deaths in females. In this group are probably included a number of infections following gangrene.

THE INCIDENCE OF CANCER IN THE DIABETIC PATIENTS

It is of interest to study the deaths from cancer in these clinic patients in more detail. We may compute the number of deaths from cancer to be expected on the assumption that the incidence of cancer is independent of that of diabetes by multiplying the number of years experienced by the death rates from cancer in the general population of Australia for each age group and summing. We have done this for each sex using the death rates from each cancer for the years 1931 to 1940. (For references, see Lancaster, 1955.) The results are given in Table V.

The total expected deaths of males from cancer were 17·37, and 22 were observed; 36·96 deaths were expected for females, and 67 were observed.

Cancer of the Pancreas.—The high incidence in these patients of cancer of the pancreas has already been commented on by Lancaster (1954) using the experience up to 1947. The additional experience confirms the previous

TABLE IVA

The Cause of Death in Clinic Diabetics, 1932 to 1952—Males

Age Group (Years)	Cause of Death											
	Total	Diabetes Unqualified	Coma	Gangrene	Arterial Degeneration	Tuberculosis	Cancer of the Pancreas	All Other Cancers	Gall-Bladder Disease	Purulent Infections	All Other Causes	Death Cause Unavailable
Under 15 ..	1	—	—	—	1	—	—	—	—	—	—	—
15– ..	15	—	7	—	1	2	—	—	—	3	—	2
25– ..	9	2	—	—	—	3	—	—	—	2	2	—
35– ..	17	2	4	—	—	1	—	—	—	4	6	—
45– ..	49	6	5	1	14	6	—	4	—	2	9	2
55– ..	93	5	2	3	45	12	3	5	—	3	15	—
65– ..	81	8	2	2	50	1	1	7	—	3	6	1
75 and over	35	3	2	1	20	2	1	1	—	—	4	1
All ages ..	300	26	22	7	131	27	5	17	—	17	42	6

TABLE IVB

The Cause of Death in Clinic Diabetics, 1932 to 1952—Females

Age Group (Years)	Cause of Death											
	Total	Diabetes Unqualified	Coma	Gangrene	Arterial Degeneration	Tuberculosis	Cancer of the Pancreas	All Other Cancers	Gall-Bladder Disease	Purulent Infections	All Other Causes	Death Cause Unavailable
Under 15 ..	2	—	2	—	—	—	—	—	—	—	—	—
15– ..	8	1	4	—	—	—	—	—	—	—	3	—
25– ..	10	2	1	—	—	3	—	1	—	—	3	—
35– ..	30	4	3	—	6	5	—	3	—	3	5	1
45– ..	85	6	4	2	33	3	2	10	1	6	15	3
55– ..	180	9	5	6	89	7	5	19	3	10	22	5
65– ..	213	8	1	11	141	3	2	21	1	11	12	2
75 and over	66	5	1	5	39	—	1	3	—	2	10	—
All ages ..	594	35	21	24	308	21	10	57	5	32	70	11

conclusion that cancer of the pancreas is associated with diabetes. Five males and ten females were certified as having cancer of the pancreas, compared with expected numbers of 0·62 male and 1·24 female.

TABLE V

The Observed and Expected Incidence of Cancer in Clinic Patients

Site of Cancer	Numbers of Cancers			
	Males		Females	
	Observed	Expected	Observed	Expected
Buccal cavity ..	1	1·60	0	0·50
Œsophagus ..	1	0·82	0	0·62
Stomach	3	5·12	7	6·98
Intestine	3	2·06	9	5·79
Rectum	1	0·92	2	1·52
Liver and bile passages ..	0	0·67	1	2·11
Pancreas	5	0·62	10	1·25
Respiratory ..	0	1·03	1	0·83
Breast	0	0·03	15	6·68
Uterus	—	—	9	4·95
Vulva and vagina ..	—	—	4	0·39
Ovary	—	—	2	1·55
Prostate	2	1·86	—	—
All other cancers ..	6	2·64	7	3·77
Total cancer ..	22	17·37	67	36·96

Cancer of the Uterus.—The larger experience suggests also that cancer of the uterus is commoner than expected in these patients—nine were certified and only 4·95 were to be expected. Way (1954) and Kimbell *et alii* (1954) find an association of diabetes with cancer of the body of the uterus. Our records do not show whether the cancer was in the body or in the cervix. In the vulva, vagina, ovary and breast the observed incidence also exceeded the expected incidence.

There appears to be reasonable agreement between the expected and observed (certified) deaths from cancer of the alimentary, genito-urinary and respiratory systems. In no other system were the deaths sufficient in number to enable a good comparison to be made.

TABLE VI

The Mortality in the Australian Population from Diabetes

Ages (Years)	Deaths per Million per Annum					
	Males			Females		
	1931 to 1940	1941 to 1945	1946 to 1950	1931 to 1940	1941 to 1945	1946 to 1950
0 to 4	9	7	5	6	7	3
5 to 14	15	9	5	13	11	8
15 to 24	14	12	7	22	20	13
25 to 34	19	14	15	20	27	17
35 to 44	39	38	25	51	42	27
45 to 54	92	94	91	172	160	103
55 to 64	335	332	293	628	639	542
65 to 74	838	856	820	1579	1757	1606
75 and over ..	1435	1639	1593	2265	2529	2601
All ages	117	129	125	211	254	244

DIABETES AS A CAUSE OF MORTALITY IN AUSTRALIA

We have previously discussed diabetes as a cause of mortality in Australia (Lancaster and Maddox, 1950) but the inspection of the death certificates of these patients will help in their proper interpretation. In Table VI we give the death rates from diabetes in Australia for the three most recent periods of the use of the old rules of the "International List of Causes of Death", when the fourth and fifth revisions were being used. There have been some declines, as had already been noted by Downie (1938), in the mortality rates, particularly at ages under 35 years in males, and under 55 years in females, but the declines have been rather small. At the higher ages over 45 years in males and 65 years in females, the rates have shown some slight increases. (The figures for the years 1941 to 1945 in Table VI amend those of Table III in Lancaster and Maddox (1950). In Figure III, we give graphically the trends in the rates from 1908 to 1950. These

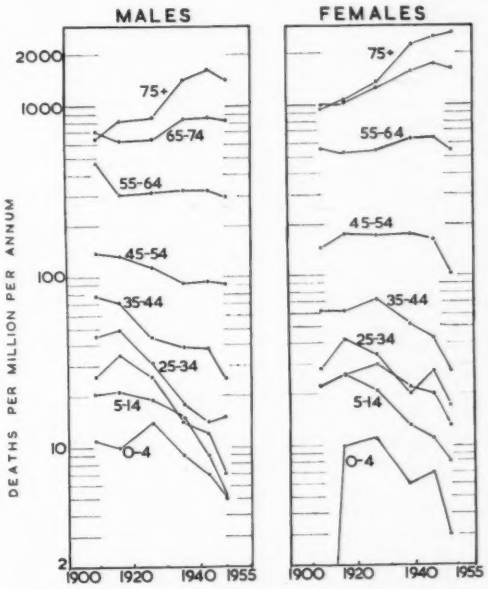

FIGURE III

The mortality from diabetes in the general population of Australia

trends have been already discussed by Lancaster and Maddox (1950) and are similar to trends in other countries, such as England and Wales and the United States of America (Stocks, 1944; Harris and MacArthur, 1951).

However, many more patients die with diabetes than are certified. In Table VII, we show that in the death certificates of 165 male and 383 female diabetic patients, diabetes was not mentioned. In a further 21 males and 32 females diabetes was mentioned in the certificate, but would not be counted as the cause of death in accordance with the rules of the "International List of Causes of Death". Thus for the deaths of 300 males and 594 females, diabetes would not be counted by the statistician as the cause of death in 186 of the males and 415 of the females. So that, of our clinic patients, only 38% of the males and 30% of the females would have their deaths coded to diabetes as the cause of death. This is lower than the proportion cited by Joslin and Lombard (1936), who found that only 60% of known diabetics had their deaths finally coded to diabetes as the underlying cause in the sense of the "International List of Causes of Death". It appears that often the certifier is more preoccupied with the mode of death than with the underlying cause. Before the official statistics can give us an adequate picture of the load of diabetes, they must be improved by some form of supervision such as exists in England and Wales or in New Zealand. In these countries, if the certificate is inadequate, a query is sent to the certifier asking him to give further details. Our own study certainly shows that diabetes is certified in Australia much less frequently than it should be, and that Australia has a true diabetes rate of much the same order as the United States of America. Now that the techniques of morbidity surveys, with or without medical examination of the subjects, are well understood, we may hope to get a better idea of diabetic prevalence and morbidity in the Australian population. The only survey yet carried out that we know of is by Lancaster (1951), who found that about 0·6% of the males and 1·5% of the females above the age of 50 years had applied for the special diabetic ration cards between June, 1944, and June, 1945.

TABLE VII

Diabetes as a Cause of Death in the Official Statistics

Disease Group	Diabetes Not Mentioned on Death Certificate		Diabetes Mentioned but Not Coded Because of Priority Rules	
	Males	Females	Males	Females
Arterial degenerations etc. ..	102	277	0	0
Gangrene	2	0	0	0
Tuberculosis ..	14	10	13	11
Cancer of the pancreas.. ..	5	7	0	3
Other cancer ..	17	51	5	13
Purulent disease ..	17	18	2	1
Other cause ..	8	20	1	4
All causes	165	383	21	32

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DIABETIC COMA : A REVIEW OF 69 CASES[1]

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SUMMARY

Sixty-nine episodes of diabetic coma occurring in the past five and a half years at the Royal Prince Alfred Hospital have been reviewed. The overall mortality rate was 16% (eleven deaths). Three deaths occurred after recovery from ketosis as a result of concomitant disease. One patient died from a combination of diabetic ketosis and cardiac failure. Two patients were moribund on admission and died soon after arrival with progressive diabetic ketosis. One patient died as a result of bilateral adrenal hæmorrhage. The remaining four patients developed circulatory failure some time after treatment commenced and died as a result of this complication. At autopsy in two of these latter patients no cause for the collapse could be found.

Factors found to be associated with a high mortality rate were age over 50 years, a blood sugar level on admission greater than 600 milligrammes per 100 millilitres, loss of consciousness and symptoms of ketosis for more than two days.

Factors which seemed to have no bearing on the outcome were the level of plasma bicarbonate, the pulse rate and blood pressure on admission, insulin resistance and the preceding insulin requirements.

No serious ill effects due to either hypoglycæmia or hypokalæmia were encountered.

Attention is drawn to the development in seven patients of sudden hypotension, tachycardia and sometimes anuria some hours after treatment had commenced. These patients were, in general, not shocked on admission and, apart from being among the more severe examples of ketosis, showed no other features distinguishing them from the rest of the series. Initial clinical and biochemical improvement proceeded normally until the collapse occurred. The mortality rate was high (four out of seven). No specific ætiological factor could be demonstrated.

MATERIAL AND DEFINITION

THE case histories of every diabetic patient admitted to the public wards of the Royal Prince Alfred Hospital between July 1, 1950, and December 31, 1955, were reviewed. A biochemical criterion was adopted, and a patient was considered to be in diabetic coma when the plasma bicarbonate level (carbon dioxide combining power) on admission was 10 milli-equivalents per litre or less. Although subject to criticism, such a criterion is similar to that used by other writers and avoids controversial problems of clinical assessment. There were 69 episodes of diabetic coma occurring in 58 patients in the period referred to. There was one patient with seven episodes of coma, one with four, two with two, and 54 with one. In two patients the plasma bicarbonate level was not estimated on admission ; they are included because of the clinical severity of their condition, the height of the blood sugar level (1020 and 635 milligrammes per 100 millilitres) and the large doses of insulin required in the first eighteen hours (810 and 750 units).

AGE AND SEX (TABLE I)

The average age for the whole group was 38·3 years. Although higher than Joslin's (1952) figure of 29·3 years, the average age is still considerably lower than that of diabetics in the general population. As in other series, there were more females—38 of the 58 patients. The mortality rate showed a distinct correlation with age. There were 48 admissions of patients under 50 years of age with one death, and 21 of patients over 50 with 10 deaths. The difference is highly significant ($\chi^2=23\cdot0$; $n=1$; $P<0\cdot01$).

TABLE I

Age at First Admission in Diabetic Coma (58 Patients)

Age (Years)	Males	Females	Total	Deaths
10—19	2	8	10	—
20—29	4	10	14	—
30—39	6	4	10	1
40—49	1	3	4	—
50—59	3	5	8	2
60—69	4	4	8	6
70—79	—	3	3	1
Over 80	—	1	1	1
Total	20	38	58	11

[1] Received on October 21, 1957.

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AGE OF ONSET OF DIABETES (TABLE II)

Of the members of the group 50% were known to have *diabetes mellitus* before the age of 30 years. The time interval between the diagnosis of *diabetes mellitus* and the onset of coma was less than two years in six cases, from two to five years in eleven, from six to ten years in ten, from 11 to 15 years in ten, from 16 to 20 years in three, and more than 20 years in two. In four cases the interval was unknown, and in 12 *diabetes mellitus* was first diagnosed when the patient presented in coma. The "younger" diabetic is more liable to coma, which may occur after many years of stabilization, but the "elderly" diabetic is not immune from severe ketosis, which indeed carries a much higher mortality rate in this group.

TABLE II

Age of Onset of Diabetes Mellitus (58 *Patients*)

Age (Years)	Males	Females	Total
Less than 10	—	3	3
10—19	5	12	17
20—29	4	5	9
30—39	4	3	7
40—49	1	5	6
50—59	3	2	5
60—69	1	5	6
Over 70	—	1	1
Unknown	2	2	4
Total	20	38	58

COMA AS THE PRESENTING SYMPTOM OF DIABETES MELLITUS

In 57 admissions the patient was a known diabetic, and six of these patients died. In the other 12 coma was the presenting symptom of the disease, and of these five died. Excluding patients who recovered from coma but died of some other condition, there was a mortality rate of 5% among the known diabetics (3 out of 54), compared with 36% (4 out of 11) among those whose coma was the presenting symptom. The difference is significant ($\chi^2=8\cdot8$; $n=1$; $P<0\cdot01$).

THE PRECIPITATING CAUSE OF DIABETIC COMA (TABLE III)

There was a large group in which no cause was apparent. Inadequate records account for some of these cases; in others, though the patient denied dietary indiscretion or cessation of insulin, these factors probably played some part. It is difficult to draw any definite conclusions concerning the role of inadequate insulin therapy, for those who admitted ceasing therapy had generally begun to feel ill before doing so.

Gastro-enteritis was accepted as a precipitating cause only when diarrhœa was present. Vomiting alone is more likely due to diabetic ketosis, and by itself does not indicate an alimentary tract infection. The classical precipitating cause—infection—was seen in little more than one-third of the episodes.

TABLE III

Precipitating Causes of Diabetic Coma (69 *Episodes*)

Cause		No.	
Upper respiratory tract infection			10
Gastro-enteritis			7
Superficial infections	cellulitis	1	6
	carbuncle	1	
	vulvitis	2	
	ischio-rectal abscess	1	
	thrombophlebitis	1	
Pyelonephritis			3
Lobar pneumonia			1
Dental abscess			1
Emotional upsets			7
Intestinal obstruction			1
Told to cease insulin by faith healer			1
Presenting symptom of *diabetes mellitus* without other cause			9
Unknown			23
Total			69

Emotional upsets seemed to play a part in the production of ketosis in seven instances. In one girl the effect of an emotional upset was observed in hospital. She was convalescing from severe diabetic ketosis and was, for her, remarkably stable. On being told that she would be going home next day she became agitated and upset, and within three hours she passed into a state of ketosis with a plasma bicarbonate level of seven milliequivalents per litre.

TABLE IV

Duration of Symptoms of Ketosis (69 *Episodes*)

Durations of Symptoms (Hours)	Number of Episodes	Deaths
Less than 12	14	1
13—24	22	—
25—48	15	3
49—72	4	2
More than 72	6	3
Unknown	8	2
Total	69	11

DURATION OF SYMPTOMS OF KETOSIS (TABLE IV)

Attempts were made to disregard the symptoms of any precipitating illness. There was a correlation between the duration of the ketosis and the mortality rate; excluding deaths due to causes other than diabetic coma, there was one death among 48 admissions where

symptoms of ketosis were present for less than 48 hours, compared with five deaths in ten admissions where the duration of symptoms was more than 48 hours. The difference is statistically significant ($\chi^2=21\cdot4$; $n=1$; $P<0\cdot01$). As stated earlier, another factor in determining the outcome was the age of the patient. If these two factors, the duration of ketosis and the age of the patient, are considered together (Table V), almost the entire mortality for diabetic coma *per se* is seen to have occurred in patients over 50 years of age who had had symptoms of ketosis for more than 48 hours.

TABLE V

Age of Patient and Duration of Ketosis Compared with Mortality Rate

Duration of Ketosis	Age (Years)	
	Less than 50	50 or more
48 hours or less ..	0 death 39 episodes	4 deaths[1] 12 episodes
More than 48 hours ..	1 death 5 episodes	4 deaths 5 episodes

[1] Three of these four deaths were due to causes other than diabetic coma.

The duration of ketosis in two patients who died and six who survived was unknown, but both of the deaths occurred in patients over the age of 50 years.

SYMPTOMS AND SIGNS OF DIABETIC COMA (TABLE VI)

Ten patients were conscious and rational on admission to hospital; frank coma was seen on only 14 occasions. The mortality rate showed some correlation with the state of consciousness, but this was far from absolute, and one patient died who had been quite conscious on admission.

TABLE VI

Symptoms and Signs in 69 Episodes of Coma

Symptoms and Signs	No.	Deaths
Vomiting	51	—
Abdominal pain	15	—
Nausea without vomiting	3	—
Backache	6	—
Severe headache	2	—
Dehydration	52	—
Odour of acetone on breath	34	—
Hyperpnœa	48	—
Disturbances of consciousness on admission:		
Coma	14	6
Stupor	14	2
Confusion	6	1
Drowsiness	25	1
Nil	10	1

Clinical estimation of the degree of dehydration is difficult and relatively inaccurate. Patients in this series manifested all degrees of fluid loss, from those with classical signs of dehydration and shock to several who did not appear dehydrated at all. One patient appeared to present an insoluble problem from this point of view. He was admitted comatose, with the general signs of dehydration, but with gross œdema of both legs, cardiac enlargement and signs of pulmonary congestion. Circulatory collapse occurred, requiring nor-adrenalin administration, but despite the use of digitalis and supportive therapy, death ensued at seven and a half hours. Autopsy revealed pulmonary œdema, cardiac dilatation, venous congestion of all organs, renal calculi and chronic pyoelonephritis, a large duodenal ulcer and a carcinoma of the penis.

Vomiting occurred in 51 episodes and must be considered a symptom of diabetic ketosis in its own right. Abdominal pain, with or without tenderness, occurred on 15 occasions, and was sometimes sufficiently severe to raise the possibility of an intraabdominal emergency. In none of these 15 patients was an intra-abdominal lesion subsequently detected. But one patient presenting the usual symptoms and signs of diabetic coma, without abdominal pain or tenderness, recovered from diabetic ketosis to die 24 hours later from unrecognized strangulation of a loop of ileum in an internal hernia.

Hyperpnœa was sufficiently marked to draw the patient's attention to it or to be noticed by the observer in 48 instances. There appeared to be no correlation between the degree of hyperpnœa and the level of plasma bicarbonate. The odour of acetone on the breath was recorded on only 34 occasions.

The pulse rate and blood pressure on admission proved to be of no help in assessing the ultimate fate of the patient. There was no correlation between hypotension and tachycardia on the one hand and mortality rate on the other, though assessment of both features was of considerable help at the time in deciding the necessary speed of intravenous infusion and the need for supportive measures. The temperature on admission was in general normal or subnormal, and only eight patients had a temperature above 99° F. when first seen. The absence of fever on admission does not exclude serious infection, for a rise of temperature to febrile levels was not uncommon after body hydration had been restored. A leucocyte count was performed on admission in one-third of the cases, and a wide variation was obvious. The highest leucocyte count apparently due to diabetic ketosis alone was 27,500 white cells per cubic millimetre.

BIOCHEMICAL CHANGES (TABLES VII AND VIII)

The level of plasma bicarbonate appeared to have no bearing on the ultimate prognosis. Indeed, it is generally agreed that it is not a good index of the severity of acidosis at low levels, hence the use by some of blood pH and serum ketone estimations, or serum Rothera reactions (Lee and Duncan, 1956). The limitations of plasma bicarbonate estimations are probably due to the inaccuracy of the method at low levels, and not, as Bland (1956) has suggested, to the possibility of a superimposed respiratory acidosis (the respiratory rate in all but two of our 65 recorded cases was over 20 per minute).

TABLE VII

Admission Blood Sugar and Plasma Bicarbonate Levels

Biochemical Determination	Number of Cases	Deaths
Level of blood sugar (milligrammes per 100 millilitres):		
200—400	14	1
401—600	27	—
601—1000	25	9
Above 1000	3	1
Plasma bicarbonate content (milli-equivalents per litre):		
5 or less	29	5
More than 5	38	6
Not estimated	2	—

The mortality rate showed a significant correlation with initial blood sugar levels. Only one death occurred among 41 patients with a blood sugar level less than 600 milligrammes per 100 millilitres, compared with 10 deaths among 28 patients with a blood sugar level greater than 600 milligrammes per 100 millilitres. These findings differ from those of Bland (1956), who does not regard the blood sugar level as a reliable prognostic criterion.

Serum potassium estimations were performed in less than half the cases. The general pattern is shown in Table VIII; high initial serum levels were followed by a fall, sometimes to very low values, as therapy proceeded with reestablishment of glycogenesis, expansion of the extracellular fluid compartment and further losses of potassium in the urine. Electrocardiograms were performed on six occasions when hypokalæmia was suspected, and in each case the tracing was consistent with that diagnosis. Two patients had admission electrocardiograms showing changes consistent with hyperkalæmia, in one case misinterpreted as indicating antero-lateral myocardial infarction. Both reverted to normal after cure of the biochemical abnormality. No case was encountered in the series with symptoms attributable to hypokalæmia, but since the conclusion of the study at least one example of generalized muscle weakness and one of paralytic ileus have been seen in the recovery phase of diabetic ketosis.

The blood urea content was determined in the first 24 hours in only 23 instances, and it was elevated in all but five. All four patients in whom the blood urea content was greater than 100 milligrammes per 100 millilitres on admission died.

INSULIN DOSAGE (TABLE IX)

Details of insulin dosage were available in 68 episodes. The doses were generally higher than Joslin's (1952) for patients with corresponding blood sugar levels. This may be due to the prior administration of insulin by the recommending doctor, which his clinic advocates. The present series is regrettably marked by the fact that very few patients had been given insulin before being sent to hospital.

Rather more than half of the 18-hour dose of insulin was given within four hours, and the amount added between 12 and 18 hours was relatively small. This is consistent with recent practice; Root (1955) has stated that if 50% to 60% of the first 24-hour dose of insulin is not given within three hours, it is not being given quickly enough.

The commonest initial dose of soluble insulin in the latter part of the period under review was 100 units given intravenously and 100 units given intramuscularly. When the blood sugar level was found to be greater than 800 milligrammes per 100 millilitres, another 50 units given intravenously and intramuscularly were usually administered at once. Subsequent doses were modified according to the patient's

TABLE VIII

Serum Potassium Levels

Stage of Determination	Serum Potassium Levels (Milliequivalents per Litre)				
	Less than 2·0	2·1—3·5	3·6—5·0	5·1—7·0	More than 7
On admission (20 cases)	—	—	2	13	5
Lowest level reached during treatment (29 cases)	3	16	9	1	—

TABLE IX

Average Cumulative Soluble Insulin Dosage Compared With Initial Blood Sugar Levels

Initial Blood Sugar Level. (Milligrammes per 100 Millilitres)	Average Cumulative Dose of Soluble Insulin (Units)			
	Initial	To 4 Hours	To 12 Hours	To 18 Hours[1]
More than 1000 (3 cases)	187	553	563	570 (825)
601—1000 (25 cases)	177	445	644	713 (526)
401—600 (27 cases)	147	298	401	419 (329)
200–400 (13 cases)	128	241	306	322 (151)

[1] The figures in parentheses are the average 24-hour doses of soluble insulin given in a series with corresponding blood sugar levels at the Joslin clinic (1946–53).
The doses of insulin given in one case are not available.

response and were with a few exceptions based on a two-hourly regime in the early phase of therapy. This has been criticized as too long a gap between doses, but there was no evidence that any patient died because of inadequate insulin in the present series.

Hypoglycæmia occurred on nine occasions. Six patients had clinical evidence of hypoglycæmia, and there were three blood sugar recordings of 53 milligrammes per 100 millilitres without accompanying symptoms. With the exception of one ten-year-old girl, who had two attacks of generalized convulsions, none of the episodes of hypoglycæmia caused any concern.

INSULIN RESISTANCE

In practice all degrees of insulin resistance were met with, for diabetic ketosis is itself a state of relative resistance to insulin in ordinary doses. The seven cases in which more than 900 units of soluble insulin were required in eighteen hours were arbitrarily designated insulin-resistant (Table X). There was an infective factor in only one of these. In general they were severe examples of ketosis, but other cases appearing equally severe clinically and biochemically did not manifest the phenomenon. Nor were the doses of insulin required prior to admission by those who were known to be diabetics excessive; indeed, one patient had been controlled well on dietary restriction alone for four years. We see no way of anticipating with accuracy those cases in which very large doses of insulin are likely to be needed.

INTRAVENOUS FLUID THERAPY

The volume of fluid administered intravenously in the first 24 hours varied enormously. The average amount was of the order of five litres, and half of this was usually given in the first four hours. It is now almost uniform practice at the Royal Prince Alfred Hospital to administer normal sodium chloride solution and one-sixth molar sodium lactate in a ratio of 3 : 2 for the first few hours of therapy. In the early period of this survey normal saline alone was the major fluid used, and it is an impression that recovery from acidosis was considerably more rapid in the later cases than in the earlier.

Glucose in distilled water was administered intravenously only after the blood sugar level had fallen below 300 milligrammes per 100 millilitres, and in this way water was made available for cellular rehydration. Early intra-

TABLE X

Cases Demonstrating Insulin Resistance

Case Number	Age	Precipitating Factor	Duration of Diabetes (Years)	Duration of Ketosis (Hours)	State of Consciousness[1]	Initial Blood Sugar Level (Milligrammes *per centum*)	Initial Plasma Bicarbonate Level (Milliequivalents per Litre)	Dose of Insulin (Units) in 18 Hours	Result
1	61	Unknown	—	72	Coma	745	9·0	1600	Died
2	62	Unknown	1	24	Coma	674	2·0	1800	Recovered
3	72	Carbuncles	4	24	Coma	542	3·0	1680	Recovered
4	56	Unknown	14	Unknown	Coma	950	2·5	1300	Recovered
5	37	Unknown	—	24	Conscious	885	2·5	980	Recovered
6	29	Unknown	11	72	Conscious	938	3·6	950	Recovered
7	72	Unknown	2	Unknown	Stupor	900	2·0	990	Recovered

[1] In cases 1 and 5 coma was the presenting manifestation of *diabetes mellitus*.

venous administration of glucose may lead to excessive extracellular osmolarity with consequent cellular dehydration, continued diuresis and further electrolyte losses in the urine; it may interfere with carbohydrate metabolism by creating very high blood sugar levels; and, as pointed out by Nabarro *et alii* (1952), it interferes with blood sugar estimations, sometimes the only indication of progress in the first few hours.

Potassium salts were more and more frequently given orally or intravenously towards the end of the series, and it is now almost routine to use them when the serum potassium level falls below four milliequivalents per litre or after four hours of satisfactory treatment. No conclusion could be drawn as to the amount of potassium needed from the figures available, but the amount given intravenously was generally between 70 and 140 milliequivalents. It is probable that in the presence of an adequate urinary output much larger amounts may be given without risk and probably with benefit.

Analysis of Deaths

Eleven patients died, a case mortality rate of 16% for the 69 admissions. Three of the deaths were due primarily to causes other than diabetic coma. In these three cases the patients recovered from their acidosis to die respectively of lobar pneumonia (four days after admission), strangulated internal hernia (24 hours after admission) and pulmonary embolism (12 hours after admission). To these should probably be added the patient mentioned earlier with gross cardiac failure, renal disease and other abnormalities. Seven cases remain in which death was directly due to diabetic coma or complications of treatment. In two the patients died rapidly in coma, one one and a half hours and one seven and a half hours after admission. Both were moribund on arrival at the hospital and perished despite administration of large amounts of fluid and insulin. A third was a woman of seventy, admitted semicomatose but but not shocked after three days of ketosis, with a blood sugar content of 616 milligrammes per 100 millilitres and a plasma bicarbonate level of seven milliequivalents per litre. A total of 350 units of insulin was administered in the first eighteen hours, by which time the ketosis was well controlled. From the second hospital day until the patient's sudden collapse and death on the fourth day she required only 20 more units of insulin. Autopsy revealed bilateral adrenal hæmorrhage.

There remain four patients who died with the ommon feature that death followed circulatory failure developing during the course of therapy. Autopsies were performed in only two of these cases. The kidneys of one showed diabetic glomerulosclerosis, while in the other the kidneys and other organs appeared normal. This mode of death is taken up in more detail in the next section.

In the first two and a half years under review, there were seven deaths among 31 cases of diabetic coma compared with four deaths among 38 cases in the last three years. The difference is perhaps more striking when it is noted that three of the four deaths in the latter period were due to causes other than the coma itself.

Circulatory Failure Appearing During the Course of Therapy

Particular attention is drawn to the development in seven patients of circulatory failure some time after the commencement of therapy. Circulatory failure is an obvious and inevitable outcome of progressive diabetic ketosis with continuing loss of body fluids and electrolytes, but circumstances here are somewhat different. It is by no means a prerequisite of this complication that the patient be shocked when first seen (Table XI), and five of the seven patients had a systolic blood pressure greater than 100 mm. Hg at the time of admission.

Events followed a fairly constant pattern. Therapy was initiated, and all seemed well with adequate blood pressure and urinary output, a falling blood sugar level and rising plasma bicarbonate level, and a patient who was improving clinically. Then, quite suddenly (and most frequently four to eight hours after commencing treatment), there developed hypotension, tachycardia, sometimes anuria and rarely abdominal pain. In two cases this collapse seemed mild at first and was relieved by the administration of methedrine, only to reappear in a more severe form later.

An attempt was made to characterize those patients who developed this complication by examining the factors shown in Table XI. Beyond the general statement that they were among those with the more severe examples of ketosis, no specific conclusions could be reached.

We can suggest no adequate explanation of the phenomenon. Joslin *et alii* (1952) and Nabarro *et alii* (1952) mention its occurrence, but group it with the hypotension seen in untreated cases. We believe this to be incorrect. The cause of pre-treatment shock is the great reduction in extracellular fluid and circulating blood volume. The form of circulatory failure under discussion occurred some hours (in one case 22 hours) after the beginning of treatment.

TABLE XI

Patients Developing Circulatory Failure During Therapy

Number	Age	Duration of Ketosis	State of Consciousness	On Admission				Lowest Potassium Level in Serum (Milli-equivalents per Litre)	Time of Onset of Collapse (Hours)	Result
				Systolic Blood Pressure (mm. Hg)	Blood Sugar Level (Milli-grammes per 100 Millilitres)	Plasma Bi-carbonate Level (Milli-equivalents per litre)	Blood Urea Content (Milli-grammes per 100 Millilitres)			
1	61	72 hours	Comatose	70	745	9·0	195	Hypo-kalæmia E.C.G.	4, and 14	Died in 24 hours
2	65	Days	Drowsy	120	608	1·0	137	—	22	Died in 41 hours
3	52	Days	Drowsy	110	320	3·0	66	—	4	Died in 15 hours
4	56	Unknown	Comatose	135	950	2·5	—	3·6	7½	Recovered
5	38	Unknown	Comatose	140	510	2·0	—	3·9	6	Recovered
6	20	72 hours	Comatose	95	858	4·5	56	2·8	5½	Recovered
7	54	48 hours	Comatose	120	648	8·0	—	1·8	4, and 16	Died in 72 hours

By the time shock supervened most, if not all, of the extracellular deficiencies in volume and content had been replaced, so that they are not considered to play a significant part.

Franks *et alii* (1947) believed that the appearance of this disturbance in three of their cases might be due to the intravenous administration of glucose in the early phases of treatment. This factor, whatever its significance, played no part in the present series, for six of the seven affected patients received no glucose intravenously prior to the appearance of hypotension.

A further possible mechanism is acute adrenal insufficiency. Although no investigations relevant to this possibility were carried out, a major argument against it is the failure of any patient to develop subsequent insulin sensitivity. Indeed, one case fell in the insulin-resistant group, and the patient was given 500 units of insulin in the five hours immediately following the onset of circulatory failure without developing hypoglycæmia. On the other hand, the presence of frank adrenal hæmorrhage in one other patient at autopsy does raise the possibility of structural or functional adrenal damage in severe diabetic ketosis.

Hypokalæmia is another possible explanation advanced. The collapse occurred in the recovery phase, when serum potassium levels are usually low, but it was impossible to correlate the manifestations with low serum potassium levels. Seven patients in the complete series had serum potassium levels less than three milliequivalents per litre with no evidence of circulatory failure. Intracellular potassium deficiency as a possible ætiological factor is difficult to evaluate. There is considerable cellular potassium loss in diabetic coma, which may perhaps reach critical levels; but at the time when this syndrome appears, glycogenesis is reestablished, potassium is returning to the cells, and cellular potassium content should be higher than it was in the initial stages when shock was absent.

Finally, there is the problem of intracellular water deficit, which Nabarro (1952) has estimated at about three litres in the moderately severe case. In the regime of therapy described no water is made available for cellular needs until extracellular deficiencies have been restored and the blood sugar level has fallen below 300 milligrammes per 100 millilitres. Bland (1956) has stressed the need for the early administration of some type of hypotonic solution by which water is made available to the cells. Intracellular water deprivation may be a factor in the production of circulatory failure during therapy, but we have no evidence to offer on the subject.

The therapy of a condition is unsatisfactory when its pathogenesis is obscure. In those cases in which circulatory failure develops during treatment the best therapy for the present is probably the judicious administration of nor-adrenalin to maintain the systolic blood pressure at or above 100 mm. Hg, in the hope that acute renal failure will not supervene. Of the seven patients who developed this complication four died. Three of the episodes occurred before nor-adrenalin became available in this country, and all three proved fatal. Among the four more recent patients given nor-adrenalin by continuous intravenous infusion one death has occurred.

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DYSTROPHIA MYOTONICA—DEATH UNDER " PENTOTHAL " ANÆSTHESIA[1]

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SUMMARY

A girl of twelve had suffered locking of the knees, lumbar lordosis and ptosis since birth. Her physical development had been generally retarded. Her maternal grandfather and her mother had both suffered " locking " of the knees and myopathy.

Various muscles showed atrophy and pseudohypertrophy, and there was myotonia of the tongue. Early cataracts were present in both eyes. Examination revealed no abnormality of the heart.

Operation for the ptosis, under " Pentothal ", ethyl chloride and open ether anæsthesia, was uneventful, but respiration ceased suddenly 30 minutes after operation, and she died 15 minutes later. At autopsy the heart showed adipose and collagenous replacement of myocardial fibres. Similar changes were present in skeletal muscles.

Cardiac involvement has been reported in 61 of 98 cases of *dystrophia myotonica* and in a further 18 of 35 previously reported by the author. It is usually manifested by electrocardiographic changes, and physical signs are rare. Such patients have been reported to be particularly prone to respiratory troubles during " Pentothal " anæsthesia. Enzymes concerned with the detoxication of " Pentothal " may be deficient in *myotonica dystrophia*.

DYSTROPHIA MYOTONICA is an hereditary familial disease transmitted by a simple dominant gene. A characteristic feature is the anticipation and potentiation of the disease with each following generation. In the first generation, cataract is usually the only sign ; and in the second generation, cataract appears at an earlier age and other features of the fully developed disease become apparent. These features include frontal baldness, myotonia, wasting of muscles, *hyperostosis cranii*, cardiac changes and endocrine dysfunction, manifested by testicular atrophy in males, and ovarian dysfunction, such as sterility and frequent miscarriages, in females. One of us (J.E.C.) has already reported on the endocrine changes, the *hyperostosis cranii* and cardiac changes in the disease.

In the third generation, the disease may present with congenital physical defects, such as cleft palate, hare lip, spastic paraplegia, syndactyly, herniæ and mental deficiency. A report of 10 cases of congenital physical defect in families with *dystrophia myotonica* was published by Caughey and Barclay (1954).

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To date, reports of the cardio-vascular system in cases of *dystrophia myotonica* have been significant because, although the electrocardiogram patterns have been abnormal, there has been a remarkable paucity of physical signs. Black and Ravin (1947) and Kilpatrick and Caughey (1955) each reported an instance in which diffuse fibrosis of the heart was noted *post mortem*.

Two cases of sudden death in patients suffering from *dystrophia myotonica* have been reported, one by Spillane (1951), who reported the case of a patient with *dystrophia myotonica* awaiting investigation in hospital who died presumably of cardiac disease, and one by Fisch and Evans (1954), who reported the case of a patient with *dystrophia myotonica* with an auricular flutter.

It appears from the literature (Dundee, 1952, 1956 ; Bourke and Zuck, 1957) that patients with *dystrophia myotonica* are unduly sensitive to " Pentothal " anæsthesia. Both Dundee (1952, 1956) and Bourke and Zuck (1957) encountered respiratory difficulties amounting to prolonged apnœa during " Pentothal " induction. Stimulation of the respiratory centre with carbon dioxide and injections of nikethamide were ineffective. One patient in a case reported by Dundee (1952) was recovering consciousness before breathing was fully restored. Dundee

concluded that the sensitivity to " Pentothal " was peripheral, probably in the muscles, and Bourke and Zuck (1957) also confirmed this finding.

We have to report a case of *dystrophia myotonica* in a young girl who died under anæsthesia. This is of interest because it indicates a grave risk of general anæsthesia in cases of *dystrophia myotonica*.

CASE REPORT

B.C., a twelve-year-old girl, was admitted to hospital in April, 1956, for neurological investigation on account of recurrent locking of the knees, lumbar lordosis and ptosis of the left eyelid.

History

The patient was an only child. Her birth weight was four and a half pounds. During the pregnancy the mother suffered from toxæmia. Drooping of the left eyelid was noted at birth. Before discharge from hospital her mother was told that the child had a " wry neck ". The child's physical development was slow up to the age of two years; her teeth started to erupt at eleven and a half months; she walked at seventeen months. At the age of twenty months the child was taken to the hospital clinic on account of a lumbar lordosis and funnel chest. Later she was admitted to the Bradford Hospital with a diagnosis of cœliac rickets and was given treatment with ultraviolet light. From the age of two and a half years onwards the child had corrective exercises for lumbar lordosis. At the age of three years locking of the knees first became apparent. Physiotherapy was continued till the patient was five years old, without improvement. She attended school and tried to take part in the school activities, but could not compete with the other girls because she was unable to run as fast as other children. Mentally she seemed to be bright and alert, and was " top of the class ".

In 1952 her parents migrated from England to New Zealand. In Dunedin she was seen at the Orthopædic Department and recommenced remedial exercises. At the age of eleven, the child put on a great amount of weight. Increased lordosis persisted, and the gait was rolling because of the weakness of the gluteal muscles. The case was thought to be one of familial dystrophy, and she was referred for neurological investigation.

Family History

Her maternal grandfather was reported to have suffered from " locking " knees, and her mother also suffered from a myopathy which caused intermittent " locking " of the knees. On examination she had increased lumbar lordosis and was unable to sit up from the supine position when her arms were folded across the chest. There was weakness of the glutei muscles, and hypertrophy of the calf and forearm muscles; no cataracts or myotonia were detected. A maternal aunt appeared to be normal. In the father and his family there were no muscular disorders known.

Past History

She had suffered from chickenpox, measles, german measles and mumps and had undergone tonsillectomy at the age of six years.

She had had no menstrual periods. There had been no headaches, no vomiting, and no excessive thirst, nor were there any symptoms referable to the cranial nerves. There was no complaint of shortness of breath, cyanosis or palpitations.

She was a short and rather obese girl with an asymmetrical face and a very marked lumbar lordosis. Her weight was five stone eleven pounds, and her height four feet six inches. The visual acuity of both the right and left eye was J.1.; the fields were full to confrontation. There was congenital ptosis on the left side, ocular movements were full, there was a fine horizontal and vertical nystagmus, the pupils were equal although slightly eccentric, and they reacted to light and accommodation directly and indirectly. Motor and sensory nerves were normal; no facial weakness was noted. Hearing was normal. The Rinné test in both ears was normal; the Weber test was referred to the left. Weakness of both sternomastoid muscles and of other neck flexors was present, but both trapezius muscles were normal. The tongue was protruded in the midline, and there was myotonia of the tongue on tapping the lateral border. There was weakness of the *serratus magnus* and deltoid muscles, and the pectoralis and triceps muscles were normal. The handgrip was firm. No active or mechanical myotonia of the hands was detected. Both the biceps and triceps reflex jerks were absent, and the supinator jerk was present on both sides. There was some weakness of the abdominal muscles, but the patient could sit up from a lying position. The lower end of the left quadriceps was atrophied, and there was pseudohypertrophy of the upper end. Both calves showed pseudohypertrophy. No active or mechanical myotonia was present. The power of the iliopsoas muscles, and of the flexor and extensor muscles of the hips and knees, was reduced, but abduction and adduction were satisfactory. Dorsiflexion of both feet was very weak. The right knee jerk was absent, and the ankle jerks were equal on both sides. The plantar response was equivocal on the right and flexor on the left. Sensation to touch, pinprick and vibration and joint position sense were normal in the arms and legs.

The pulse rate was 72 per minute and was regular. The blood pressure was 100/65 mm. Hg. The apex beat was not palpable, and the heart sounds were clear and regular. Clinically the chest was normal.

Examination of the urine showed the presence of some sugar (the finding in Benedict's test was green). X-ray pictures of the skull and chest were normal. Electrocardiography showed sinus arrhythmia, but otherwise the electrocardiogram was within normal limits. Slit lamp examination of the eyes revealed normal fundi, and the right lens showed a few tiny white particles scattered round, forming an adult nucleus with larger white marks at the junction of the embryonic and anterior portion of fœtal nuclei. The left eye showed a similar appearance. These changes were consistent with early myotonic dystrophy.

It was concluded, that in view of the family history, the congenital defects, the cataracts and the state of the musculature, the patient was suffering from *dystrophia myotonica*.

The girl left hospital and was readmitted three months later under the care of Dr. Roland Wilson, for correction of ptosis of the left eyelid. Operation took place on July 17, 1956, under general anæsthesia. Premedication of " Seconal ", two and a quarter grains (135 milligrammes), was given one and a half hours before operation, and atropine sulphate, one one-hundredth grain (0·6 milligramme) half an hour preoperatively.

Anæsthesia was induced with 200 milligrammes of intravenous " Pentothal ", followed by five millilitres of ethyl chloride and open ether. Anæsthesia was maintained by ether and oxygen through an Ayres T-piece. Throughout the operation no difficulty was experienced with respiration. Slight transient cyanosis occurred when the patient's neck was flexed to enable bandaging of the eye. The patient returned to the ward in a satisfactory condition. However, thirty minutes later she stopped breathing, and she died forty-five minutes after operation, in spite of cardiac massage and insufflation of the lungs.

Post-Mortem Report

The body was that of an obese young girl measuring 137 centimetres in length, examined approximately nineteen hours after death.

The heart weighed 220 grammes. The myocardium of the left ventricle measured 1·1 centimetres in basal thickness, and the right 0·1 centimetre. Macroscopically there were numerous obvious extensions of epicardial adipose tissue extending into the right ventricular wall to the endocardium. Histological sections of the right ventricle showed appreciable adipose and collagenous replacement of myocardial fibres. The muscle fibres themselves showed no detectable abnormality. One section from the intraventricular septum showed some focal collagenous replacement of muscle, while sections from the left ventricular wall appeared normal. The valves, coronary arteries, pulmonary artery and aorta were normal.

The œsophagus showed diffuse, marked lymphoid hyperplasia of the pharynx. The liver weighed 1100 grammes and showed moderate fatty change, and the left lobe showed considerable bruising.

In the kidneys, the capsules were not adherent, and the exposed surfaces showed a few shallow congenital grooves. Histological sections were normal.

The breasts were normal, and the ovaries well developed and normal.

The pituitary gland was normal, and the findings on histological examination were also normal. The thyroid, thymus and adrenals were normal.

The skull showed a patchy thinning. Histologically there was obliteration of the medullary space between the two tables. The whole thickness of the skull comprised dense cortical bone which appeared to be avascular and almost acellular. The macroscopic thinnings were merely focal thinnings of the bone with no corresponding structural alterations. The brain weighed 1320 grammes, and there was minimal œdema.

The muscles of the upper part of the thigh were bulky and fleshy, but around the knee joint they gave way to atrophied, shrunken and heavily fibrosed muscle. This was most striking in the belly of the *vastus medialis*, where in the region of its attachment there were only a few muscle fibres embedded in fibrous tissue. Histological examination of sections showed some variability in size and staining of muscle fibres with extensive replacement by collagenous tissue, and in some muscles, adipose replacement.

In the knee joints there was flattening of the lateral femoral condyles. On the left side, the articular cartilage extended upwards and outwards over the condyle with the formation of a new articular facet. There was roughening and osteophytosis of the lateral margin of the condylar articular cartilage. The spine showed a marked lordosis. The vertebral column appeared quite flexible.

Summary of Pathological Findings

1. *Dystrophia myotonica* with adipose infiltration of cardiac muscle.
2. Skeletal musculature with changes typical of a muscle dystrophy.
3. Lymphatic hyperplasia of the pharynx with a normal thymus gland.
4. Sclerosis of the skull.

DISCUSSION

In the last decade, increasing attention has been paid to the abnormalities of the cardiovascular system in cases of *dystrophia myotonica*. De Wind and Jones (1950) reviewed 98 cases of *dystrophia myotonica* reported in the literature, and found 61 cases which showed abnormalities in electrocardiograms.

In the series of 35 cases collected by Kilpatrick and Caughey (1955), abnormal electrocardiogram recordings were found in 18 patients. The electrocardiogram abnormalities were: prolonged *P–R* interval (more than 0·2 second), elevated concave *S–T* segement, and prolonged *Q–T* time. Other changes were left bundle branch block, ventricular ectopics and auricular flutter. The results of physical examination and fluoroscopy screening were negative in all but two cases. One patient had aortic regurgitant murmurs, and another suffered from congestive heart failure, for which no cause could be found. Autopsy examination in two cases showed no gross abnormality, although diffuse superficial fibrosis of the heart was reported in one of the cases.

Black and Ravin (1947) reported on five cases of *dystrophia myotonica* which came to autopsy. In only one case, in which the subject had presented with ante-mortem signs—distant heart sounds, a blood pressure of 104/72 mm. Hg and an abnormal electrocardiogram (elevated *S-T* segment)—was there histological variation in the size of the heart fibres.

Fisch and Evans (1954) reported on a case of sudden death in *dystrophia myotonica*. Electrocardiogram during the patient's lifetime had shown auricular flutter. In this case at autopsy, the heart was found to be dilated and histologically there was fatty infiltration of the left atrial wall, with diffuse fibrosis of the left ventricular wall and of the papillary muscle. Muscle fibres were hypertrophied, with large rectangular nuclei, and connective tissue was greatly increased in amount. Wrage and Mertens (1955) reported on similar changes in the heart muscle in a patient with *dystrophia myotonica*.

In our case, adipose infiltrations and fibrosis of the right ventricular wall and focal fibrosis of the intraventricular septum were found;

although the left ventricular wall was surprsingly normal, which might perhaps account for the essentially normal electrocardiogram recording and the paucity of the clinical signs. It seems that in this case, the heart muscle was involved in the same dystrophic process as the skeletal musculature.

Dundee (1952 and 1956) and Bourke and Zuck (1957) reported on the risk of " Pentothal " anæsthesia in patients with *dystrophia myotonica*. Dundee (1956) points out that the damaged myocardium is very susceptible to single or repeated doses of " Pentothal ", as it can produce cardiac arrhythmias.

Another point of interest is that thiopentone (" Pentothal ") detoxification in the body depends largely on the presence of certain enzymes, such as cytochrome C, adenosine triphosphate, nicotinamide and a substrate: citrate, ketoglutarate, formate, malonate. Inhibition of the phosphocreatine synthesis by 2·4 dinitrophenol decreases the " Pentothal " metabolism by 30%, which suggests that other oxidative processes are involved in metabolism of " Pentothal ".

Tower *et alii* (1956) reported on quantitative deficiency of certain enzymes involved in oxidation process in the patients with *dystrophia myotonica*, such as muscle aldolase 50% of normal, phosphorylase 35% of normal, phosphoglucomutase 50% of normal and lactic acid production 25% of normal. He also noted increased excretion of ribose in the urine, and increased excretion of creatine in urine has been known for a number of years.

Thus in our case, we have at least three factors to consider as contributing to the cause of death.

1. Undue sensitivity of the skeletal musculature.

2. Damaged myocardium.

3. The possible interrelationship of the metabolism of " Pentothal " and certain enzyme deficiencies in *dystrophia myotonica*.

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THE ARGENTAFFIN CARCINOMA SYNDROME[1]

D. R. HAY[2]

SUMMARY

A case of the argentaffin carcinoma syndrome is recorded. Attacks of trembling, sleeplessness and dyspnœa at night had been present for 14 years, and laparotomy 12 years before her death showed significant abnormalities in the intestine. Symptoms had been present for at least fourteen years, and in the terminal stages typical skin changes, asthma, diarrhœa, borborygmi, hepatomegaly and tricuspid valve disease were present. Œdema, oliguria and sweating were also prominent symptoms, and there was a high urinary excretion of 5-hydroxyindoleacetic acid.

IT is now thirty years since Pierre Masson postulated that enterochromaffin tissue possessed an endocrine function (Masson, 1928), but it is only since 1954 that clinical confirmation of this hypothesis has been established. Since the original publications of the Malmo group (Biorck *et alii*, 1952; Thorson *et alii*, 1954), about sixty cases of the argentaffin carcinoma syndrome have been reported from many parts of the world. Attacks of flushing, patchy cyanosis and erythema of the skin, asthma, diarrhœa, pulmonary and tricuspid valve disease are the clinical features of the full syndrome, which may now be confirmed by the estimation of the urinary excretion of 5-hydroxyindoleacetic acid. Several techniques are available for this investigation (Sjoerdsma and Udenfriend, 1955; Jepson, 1955; Macfarlane *et alii*, 1956).

The following is an account of a patient with this disease.

CASE REPORT

Mrs. M.L.Y., a housewife, aged 53 years, with four children, was admitted to the Christchurch Hospital under Dr. H. R. Donald on May 7, 1957, for investigation. For two years she had suffered from increasingly frequent attacks of asthma, which occurred mainly at night and after meals. At first the asthma had been relieved by simple antispasmodics, but these later became ineffective and in October, 1956, prednisone therapy was commenced with temporary improvement. Her exercise tolerance decreased, and she complained of much fatigue and palpitations on effort. At the time of her admission to hospital, the symptoms which troubled her most were diarrhœa and profuse night sweats. The latter was unaccompanied by flushing, but she was conscious of marked "gooseflesh" in her limbs. Since May, 1957, she had passed frequent loose, watery motions many times during the day and night. There was no accompanying abdominal pain, but she had noticed loud abdominal "gurglings" ever since an operation in 1943. These borborygmi were a constant embarrassment to her and were audible to others. In 1956, she first noticed bright red flushing of the face, particularly after meals and emotional upsets, but not after alcohol. Her hands and chin also became quite blue for short periods, and small blotchy red areas appeared on the hands, face, and neck. Often her eyelids were swollen in the mornings, and she thought she was passing less urine. Her legs had swollen on occasions, and she had lost two stone in weight in nine months.

In the past, she had had a thyroidectomy in 1931, and in 1934 she had been admitted to hospital because of sleeplessness, palpitations, dyspnœa and trembling at nights. A chest X-ray picture and an electrocardiogram were normal, and the attacks were attributed to anxiety. In 1943, she was admitted during the fourth month of pregnancy with a history of sudden abdominal colic, vomiting and giddiness. At laparotomy, there were found some masses of gelatinous exudate; about three feet of the small bowel was reddened and inflamed, with "miliary tubercles" on the peritoneal surface. One "old white contracted ulcer" was present in the ileum. Numerous mesenteric glands were enlarged and calcified. She was considered to have tuberculous peritonitis, but made a uneventful recovery without further treatment, and the pregnancy continued normally.

She was next admitted to hospital in January, 1956, with a brief history of colicky abdominal pain, vomiting and constipation. Apart from some lower abdominal tenderness and increased bowel sounds, no abnormality was found, the liver and heart in particular being apparently normal. A diagnosis was made of subacute small bowel obstruction due to adhesions, and she was treated conservatively. She recovered quickly except for a brief period of diarrhœa.

On examination in May, 1957, she was a thin, nervous patient of average intelligence. Her facial appearance varied greatly but was usually a dusky or ruddy colour with at times a striking cyanosis of the chin. There were conspicuous telangiectases over the cheeks. The skin of the trunk showed a bright erythema, which blanched noticeably on pressure, but gave a normal triple response to scratching. The limbs were wasted, with dry wrinkled skin but no œdema. The radial pulse was rapid and regular, with a reduced volume and a blood pressure of 135/70 mm. Hg. There was a considerable rise in venous pressure, an obvious systolic pulsation reaching to the angle of the jaw with the patient sitting upright. The chest wall was wasted, but neither ventricle was palpable and there was no thrill. On auscultation, a systolic murmur of moderate pitch and intensity was heard at

[1] Received on October 28, 1957.

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all areas, loudest in the third and fourth left interspaces. The murmur appeared to fill systole and was not influenced by respiration. At times a presystolic sound and murmur were audible at the left sternal edge, giving a triple cadence to the heart sounds. The second sound at the pulmonary area was diminished in intensity, and no splitting could be detected.

She was dyspnœic at rest but not centrally cyanosed. During inspiration the sternum was retracted inwards, and slight stridor was audible. The chest movements were limited, and sibilant rhonchi were usually present. The liver was large and nodular, being about three to four finger breadths below the costal margin. No other masses were palpable, and there was no ascites. The bowel sounds were unusually loud and active. The optic fundi and nervous system were normal.

Investigations

The results of blood count were normal except for an erythrocyte sedimentation rate of 17 millimetres per hour. Examination of the urine showed a large increase of urobilin; otherwise it was normal.

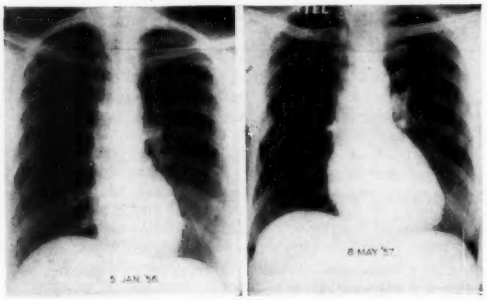

FIGURE I

Progress X-ray pictures showing the change in heart size during one year's interval. The superior *vena cava* is abnormally conspicuous in the second picture

Liver function tests gave normal results except for a prothrombin concentration of 53%.

Chest X-ray examination (Figure I) showed a slight increase in the transverse diameter of the heart from the previous year, a conspicuous superior *vena cava* and normal pulmonary vascular shadows. Fluoroscopy showed no significant ventricular enlargement; the main pulmonary artery appeared small.

The electrocardiogram was within normal limits.

The phonocardiogram demonstrated an atrial sound and a systolic murmur, loudest in late systole.

The report on a liver biopsy (Dr. D. T. Stewart) (Figure II) was as follows:

> There are two small areas of fibrosis and in these areas there is infiltration by cords of polyhedral cells showing an occasional small acinus formation. The argentaffin reaction does not stain these cells in any striking fashion. However, the appearances are suggestive, but not diagnostic of infiltration of the liver by argentaffin carcinoma.

The urine contained approximately 180 milligrammes of 5-hydroxyindoleacetic acid (5HIAA) in 24 hours (normal three to 14 milligrammes), as well as small amounts of methyltryptamine and indoleacetic acid. The method of Macfarlane *et alii* (1956) was used for this test.

Progress

The question of laparotomy was considered but rejected in view of the advanced hepatic and cardiac disease, and because there is no convincing evidence that removal of the primary growth has any symptomatic benefit in this syndrome. Prednisone

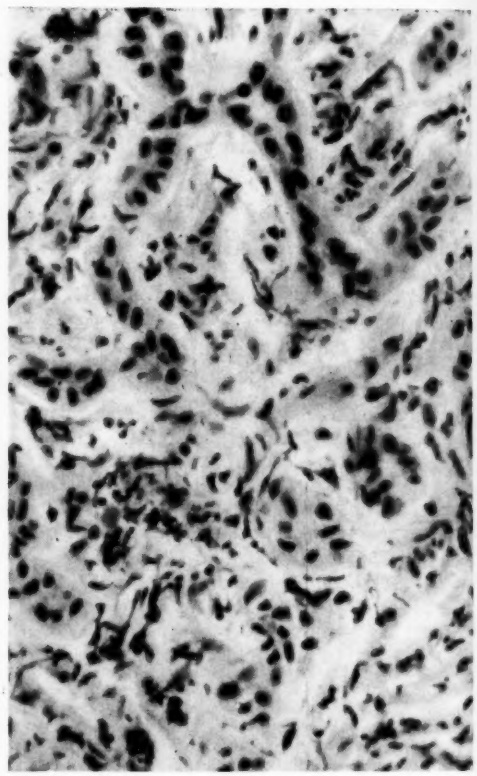

FIGURE II

Liver biopsy, showing strands of polyhedral cells with occasional acinus formation in a fibro-cellular stroma. Hæmatoxylin and eosin. High power

therapy was discontinued, and certain drugs were used which *in vitro* are known to be antagonists of 5-hydroxytryptamine (5HT). Ergotamine tartrate was without effect, but chlorpromazine temporarily relieved the diarrhœa, as did propantheline. Further trials were not possible as the patient wished to leave hospital.

After her discharge the patient's condition deteriorated steadily until her death on September 5, 1957. Generalized severe œdema developed and was probably due to the low urinary output as well as the cardiac and hepatic disease. The murmurs remained unchanged, the asthma and sweating lessened, and the diarrhœa became worse. Her attacks of flushing were

less frequent, but the permanent cyanotic patches on her chin and neck were even more striking. There were no significant mental changes.

She died at home on September 5, 1957, and permission for necropsy was refused.

DISCUSSION

Clinical

In its late stages the argentaffin carcinoma syndrome presents a characteristic clinical picture, which should allow prompt diagnosis if the disease is considered. The most important features are the large nodular liver, which is almost invariably present, and the history of changes in skin colour. The episodic character of the latter have perhaps been overstressed, for in the terminal months of the illness it is the persisting patches of cyanosis, the telangiectases and the general erythema of the skin which are most striking. Sweating has seldom previously been mentioned as a feature of the syndrome, but was a very conspicuous symptom in the case described. It is also possible that the patient's oliguria and œdema were manifestations of the renal effects of 5-hydroxytryptamine as suggested in other patients by Sinclair (1957) and Smith *et alii* (1957), and in animals by Erspamer (1954, 1955).

Biochemistry

The active hormone concerned in this syndrome, 5-hydroxytryptamine (5HT), is derived from tryptophane in the diet and ultimately metabolized to 5-hydroxyindoleacetic acid (5HIAA). As in some other reported cases (McNeely and Jones, 1946; Thorson *et alii*, 1954; Smith, 1957), there were some features of pellagra in this case, a possible explanation for which is the diversion of the dietary tryptophane to the formation of 5HT at the expense of nicotinic acid.

The urinary excretion of 5HIAA in this case was similar to that of other reported cases (Page *et alii*, 1954; Goble *et alii*, 1955; Macfarlane *et alii*, 1956; Sjoerdsma *et alii*, 1957; Pernow and Waldenstrom, 1957), but, as others have pointed out, the amount of 5HIAA excreted is not always associated with a constant clinical picture. There are in fact many conflicts between the clinical and experimental effects of 5HT, so that one wonders whether other humoral substances are concerned in the syndrome. In a second case of argentaffin carcinoma without hepatic metastases seen at Christchurch this year, there was a normal urinary excretion of 5HIAA, with no clinical symptoms or signs of the syndrome. It is of interest that large amounts of urobilinogen in the patient described interfered with the urine screening test of Hansen and Serin (1955).

The Cardiac Pathology

This case provides further evidence for the acquired nature of the valvular disease, for both clinical and radiological signs of tricuspid valve disease appeared within a year. The absence of necropsy examination made it impossible to be certain of a pulmonary valve lesion, but on the evidence from the literature it is likely that some pulmonary stenosis was present. This combination of acquired organic tricuspid and pulmonary valve disease is unique in cardiology, and presents some difficulties in bedside diagnosis. Pathological examination in other cases has shown that there is a great increase in acellular fibrous tissue, not only in the valve cusps, which become distorted and thickened, but also in the form of patchy fibroelastosis in the endocardium of the right atrium and ventricle. The changes are well illustrated in the papers of Spain (1955), Goble *et alii* (1956) and McKusick (1956).

The pathogenesis of the valvular disease is uncertain, but it is likely that the right-sided location of the pathology is related to a high concentration of 5HT reaching the right side of the heart from the hepatic metastases. This substance is destroyed by amine oxidase during its passage through the lungs, and thus the mitral and aortic valves tend to escape damage (Goble *et alii*, 1955; Waldenstrom and Ljungberg, 1955). McKusick (1956) has reported a case in which mitral and aortic disease was attributed to the shunting of 5HT-rich blood through a patent *foramen ovale* to the left side of the heart. Sjoerdsma *et alii* (1957) were unable to confirm any difference in 5HT concentration in mixed venous and arterial blood. It seems possible that 5HT stimulates the formation of fibrous connective tissue, not only in the endocardium, but also in relation to the primary tumour itself, and less commonly in other sites, for example, the pelvis (Cassidy, 1931; Hedinger and Glorr, 1954).

The Primary Tumour and Prognosis

Argentaffin tumours may occur in any part of the alimentary tract, but except in the appendix seldom produce local symptoms. They are frequently multiple, and Pearson and Fitzgerald (1949) in a review of pathological records have found that there is a significantly higher incidence of other forms of malignant disease in association with them. Numerous examples have been recorded of long survival after the demonstration of hepatic metastases from argenaffin carcinomata, and by no means all such cases develop the characteristic syndrome. No satisfactory treatment exists

except surgery, but it is to be hoped that a clinically effective antagonist to 5HT will be developed. Results so far have been disappointing.

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BOECK'S SARCOID WITH INVOLVEMENT OF THE HEART.[1]

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SUMMARY

There have been 37 recorded cases of myocardial and two of pericardial sarcoidosis. The diagnosis was made clinically in seven cases and at autopsy in 32. Twelve patients died from primarily cardiac causes, eight suddenly and four in cardiac failure. Abnormalities of rhythm and condition were recorded in 11 patients. The condition is exceedingly rare in the white races, the first case being reported in 1951.

The case history and autopsy findings are presented of a 38-year-old male who died of pulmonary and cardiac sarcoidosis in May, 1956. The illness commenced with morning cough in 1953, when X-ray examination showed opacity in both lung fields. In 1954 he began to suffer recurring attacks of dyspnœa, cyanosis and syncope due to paroxysmal ventricular tachycardia. Electrocardiograms showed right bundle branch block and there was progressive deterioration in the *T*-wave voltage.

The arrhythmia was controlled partly by procaine amide and by quinidine, but these eventually became ineffective. Cortisone therapy was continued for two years. Pulmonary lesions appeared to clear, and the arrhythmia was improved, but recurred on several occasions when the dosage was tapered off.

CLINICAL and pathological features have been recorded in 39 cases of cardiac sarcoidosis. Bernstein *et alii* (1929) record one case showing no clinical evidence of cardiac dysfunction but with pericardial and myocardial lesions found at autopsy. Salvesen (1935), recording two cases, found in the first case repeated paroxysms of tachycardia and *T*-wave abnormalities in the electrocardiogram, while in the second case constant tachycardia was present with transient right bundle branch block and premature beats in the form of bigeminy. Schaumann (1936) reports one case, in which death occurred from pulmonary heart disease, and multiple pericardial lesions were found at autopsy. Nickerson (1937) also reports the case of a 58-year-old Negress, who died of acute sarcoidosis. Multiple pericardial lesions and solitary lesions in myocardium and subendocardium were found at autopsy. Spencer and Warren (1938) report a case in which death occurred from generalized sarcoidosis, but there was no previous clinical evidence of cardiac dysfunction. Multiple microscopic sarcoid lesions of the myocardium were found at autopsy. Cotter (1939) records the case of a 19-year-old Negro who showed varying abnormalities of cardiac mechanism including tachycardia, auricular fibrillation and complete heart block. He died of cardiac failure. Extensive myocardial infiltration with large sarcoid lesions were found at autopsy.

Longcope (1941) discusses six cases, in five of which the patient showed some evidence of myocardial damage in life. In Case I no clinical evidence of cardiac dysfunction was present in life, but scattered sarcoid nodules in the myocardium were found at autopsy. In Case II, a 29-year-old Negro showed cardiac enlargement and died finally of congestive heart failure. The electrocardiogram showed numerous extrasystoles, a *P-R* interval of 0·26 to 0·28 second, and bundle branch block. No permission for autopsy was granted. In Case III a 20-year-old Negro showed cardiac enlargement and congestive heart failure, together with right upper lobe pneumonia and a pleural effusion. The electrocardiogram showed *T*-wave changes indicating myocardial damage. He finally recovered with fibrosis of the upper lobe of the right lung. In Case IV a 42-year-old Negro showed cardiac enlargement, complete atrioventricular dissociation for 10 years, extrasystoles, Stokes-Adams' syndrome and aortic incompetence. He had a positive Wassermann reaction despite seven years' therapy. He finally committed suicide. Multiple sarcoid nodules were found in the myocardium and pericardium at autopsy. There was a large dense scar in the interventricular septum, but no evidence of syphilitic aortitis. In Case V, a 40-year-old Negro dropped dead in apparent good health. Extensive infiltration of the pericardium by sarcoid masses was demonstrated at autopsy. In Case VI, a patient who had some cardiac enlargement, but was

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said to be in good health, died suddenly. Extensive invasion of the myocardium by sarcoid was noted at autopsy.

Johnson and Jason (1944) describe one case, that of a 24-year-old Negro, who showed cardiac enlargement and congestive heart failure. He showed varying disturbances of rhythm, including paroxysmal ventricular tachycardia and multiple premature ventricular beats. When he died suddenly in hospital, multiple sarcoid lesions in the pericardium and myocardium were found at autopsy.

Skavlem (1946) and Hauser (1946) describe two cases in which deaths were not due to heart lesions, but cardiac sarcoid was found at autopsy. Literature and other details of these cases reported by Skavlem and Ritterhoff (1946) are not available. McCort *et alii* (1947) describe a 31-year-old white man with generalized sarcoidosis who developed a pericardial effusion which required aspiration four times. He became asymptomatic and was discharged after 11 months. Bates and Walsh (1948) report the case of a 31-year-old Negro in whom autopsy after sudden death showed myocardial sarcoid, and similarly Scotti and McKeown (1948) record the case of a 36-year-old Negro in whom autopsy after sudden death showed multiple myocardial sarcoid lesions in the form of microscopic hard tubercles. Ricker and Clark (1949) further report the case of a 24-year-old Negro in which autopsy after sudden death showed myocardial sarcoid. In their 22 autopsy cases of sarcoidosis, there were two other typical examples of sarcoidosis of the myocardium. Kulka (1950) describes the case of a 26-year-old Negress in which autopsy after sudden death showed macroscopic myocardial sarcoid. Yesner and Silver (1951) report a case in a man, aged 51 years, the first white man to be reported as dying of cardiac sarcoidosis. He showed recurrent congestive heart failure with cardiac enlargement. The electrocardiogram showed a *P-R* interval of 0·24 second, *T*-wave inversion, *ST*-segment depression and auricular flutter. At autopsy extensive sarcoid lesions were present in the myocardium and interventricular septum. Garland and Thompson (1933) report a case in which there was "proliferative and non-caseating tuberculosis" with massive involvement of the pericardium and myocardium. Jonas (1939) records a patient who was subject to recurrent paroxysmal tachycardia and who had a negative tuberculin reaction. In this case "granulomatous myocarditis" was found at autopsy. Jonas's case, together with that of Garland and Thompson, satisfies the requirements for a diagnosis of sarcoidosis, but illustrates the difficulty which arose from lack of uniformity in diagnostic criteria in sarcoid disease.

In addition to the case of Garland and Thompson (1933), three other recorded autopsies of patients with the syndrome of uveo-parotid fever showed more or less extensive sarcoid infiltration of the heart. Souther (1929), Granstom *et alii* (1946), Mylius and Schurmann (1929).

Longcope and Freiman (1952), in a large comprehensive article entitled "A Study of Sarcoidosis", review 18 autopsies in cases of sarcoidosis from Massachusetts General Hospital and report heart involvement in two in the form of a few scattered microscopic lesions. These are reviewed in conjunction with a similar series from the Johns Hopkins Hospital of 12 autopsies, in which the heart was affected in five cases. There were a few microscopic scattered foci in three, but the myocardium was heavily invaded in two. One of these has been described previously by Jonas (1939). The case not previously described was that of a Negro, aged 40 years, who dropped dead in supposed good health. Autopsy showed widespread sarcoidosis including massive infiltration of the pericardium and myocardium. In the Johns Hopkins series, a case of clinical myocardial sarcoidosis is included, in which a 28-year-old Negress who had following uveo-parotid fever of moderate severity developed shortness of breath with cardiac enlargement and numerous extrasystoles. Skin biopsy confirmed a diagnosis of sarcoidosis.

Meyer and Ackerman (1950), from their series of 28 cases of sarcoidosis, describe two with notable clinical irregularities. In one there was transient complete heart block and in the other a "shifting pacemaker" with periods of normal rhythm. Cowdell (1954) describes the case of a 21-year-old girl at Oxford, who died suddenly and who showed at autopsy sarcoid granulomata in the form of numerous discrete rounded foci throughout the myocardium, and particularly in the subpericardial region. There was widespread pulmonary involvement as well as involvement of lymph nodes and abdominal viscera.

THERAPY IN SARCOIDOSIS

Longcope (1941) states: "Without knowledge of the cause all methods are entirely empiric. Various arsenicals, leprosol, tuberculin, roentgen rays, radium and ultra-violet rays have all been employed. We have as a routine method used ultra-violet rays which appear to be harmless and which, we believe, influence the enlargement of the superficial lymph nodes and

lesions of the skin, as in some instances these have receded."

McCort *et alii* (1947) treated two sarcoidosis patients with intrathoracic lymphadenopathy by means of high-voltage roentgen therapy. In neither of these cases was there an observable benefit radiologically or clinically. Curtis *et alii* (1947) reported considerable improvement, following large doses of both calciferol and dihydrotachysterol. Anning *et alii* (1948), treating patients with large doses of calciferol, included in their series 20 patients with sarcoidosis. Toxic reactions were common and renal damage was particularly evident. Scadding (1950) attempted treatment with calciferol in nine patients with pulmonary sarcoidosis. All six patients who tolerated calciferol showed some degree of improvement. Renal function was very carefully supervised. Gray (1950) states that the best results so far have been obtained by the administration of chaulmoogra oil preparations or sodium morrhuate over a considerable period of time. There can be no doubt that lesions gradually disappear under this treatment, but there is some tendency to recurrence.

The effect of cortisone and corticotrophin consists essentially of inhibition of granulation and connective tissue formation and involution of lymphoid tissue. With a view to reversing that process before pulmonary fibrosis and emphysema have occurred, workers have used cortisone in the early stages of granulomatous pulmonary disease.

Sones *et alii* (1951) used intramuscular cortisone therapy for two Negresses with sarcoidosis. Superficial glands disappeared or became barely palpable. Roentgenograms of the lungs showed disappearance of the bilateral miliary type of infiltration and a marked decrease in the size of hilar shadows. Siltzback and Posner (1951) reported a case of a 30-year-old Negress with pulmonary sarcoidosis and bilateral uveitis. Disappearance or shrinkage of hilar glands occurred with this treatment. The lymph node enlargement did not recur during six months of subsequent study. Lovelock and Stone (1951) report two cases of Boeck's sarcoidosis in which cortisone was given intramuscularly with marked pulmonary clearing demonstrated in chest roentgenograms, and Small (1951) similarly reports three further cases with striking regression of pulmonary symptoms and X-ray findings as in the previous cases.

The increasing use of cortisone is illustrated by Israel *et alii* (1954) in 36 patients observed as long as 46 months after treatment.

Complete roentgenological clearing of pulmonary lesions and clinical recovery occurred in three patients with astonishing rapidity. One patient relapsed after cortisone therapy was ended and required a second course.

Definite X-ray improvement with marked clinical amelioration was observed in 17 patients. The disease was not significantly influenced in 12 patients, and it proved fatal in four additional patients. Tuberculosis has not developed in any of the treated group.

Hoyle *et alii* (1955) undertook a trial of cortisone therapy combined with streptomycin and p-aminosalicylate (PAS) in 20 cases of pulmonary sarcoidosis and of streptomycin and PAS alone in a further 30 cases. With cortisone fairly rapid improvement in radiographic appearance occurred in 17 out of 20 cases.

It is evident from this survey of the literature that no records are available to indicate the appropriate management of myocardial cases, except the indication based largely on evidence from chest films that cortisone is likely to affect lesions favourably.

THE HISTORY OF A CASE OF SARCOIDOSIS WITH INVOLVEMENT OF THE HEART

The patient was a white male, aged 38 years. It is recorded that his blood pressure for insurance purposes was 140/90 mm. Hg in 1948. Since early 1953 he had suffered from a persistent morning cough with moderate sputum. He had smoked 40 to 50 cigarettes daily for the previous six years, and the cough diminished after a reduction in tobacco consumption in September, 1953. In a chest X-ray film in September, 1953, extensive abnormal opacities were noted in both lung fields with enlarged hilar shadows and heart enlargement. Serial chest X-ray films showed no change in February and April, 1954. Blood counts showed no abnormality, except for sedimentation rate elevation to 30 mm. in one hour (September, 1953) and 19 mm. in one hour (January, 1954). There were no tubercle bacilli in a direct smear examination of sputum, and the results of Mantoux tests were negative with both 1 : 1000 and 1 : 100 human tuberculin.

Since New Year, 1954, he had noticed when sitting quietly some attacks of slight breathlessness, lasting two or three minutes. In the late afternoon on February 16, 1954, he suddenly became breathless at his desk, and this symptom with unsteadiness and blurring of vision lasted half an hour. In the early evening of February 19, 1954, after standing in an overheated room, he staggered from the meeting pale, sweating profusely and with darkly cyanosed ears and lips. He recovered in half an hour and drove his car 15 miles home.

On February 20, 1954, he was first seen in consultation. He was a well-nourished man of ruddy complexion. An average blood pressure reading was 112/76 mm. Hg. There were numerous ectopic beats on a background of regular rhythm. A widely split second sound was heard in all areas. No lymphatic, splenic or hepatic enlargement was found, neither were any skin lesions present. In the subsequent investigations Wassermann and flocculation (VDRL)

tests, serum protein estimations and a liver biopsy by puncture on March 9, 1954, showed no abnormality. Electrocardiography on February 20, 1954, and a week later gave identical tracings of a right bundle branch block pattern with well marked *T*-wave inversion of a symmetrical type from lead V1 to lead V4 and small *T*-wave inversion in lead V5 (Figure I).

A clinical diagnosis of pulmonary and myocardial sarcoidosis was clearly acceptable at this stage, and he was advised to live a quiet "sanatorium type" of life at his home for an extended period.

Cortisone therapy was commenced on May 1, 1954, at the rate of 100 milligrammes daily after an initial loading dose of 200 milligrammes daily for two days. This dosage level was reduced to 75 milligrammes daily from November 4, 1954, and reduction continued to a level of 25 milligrammes daily in February, 1955.

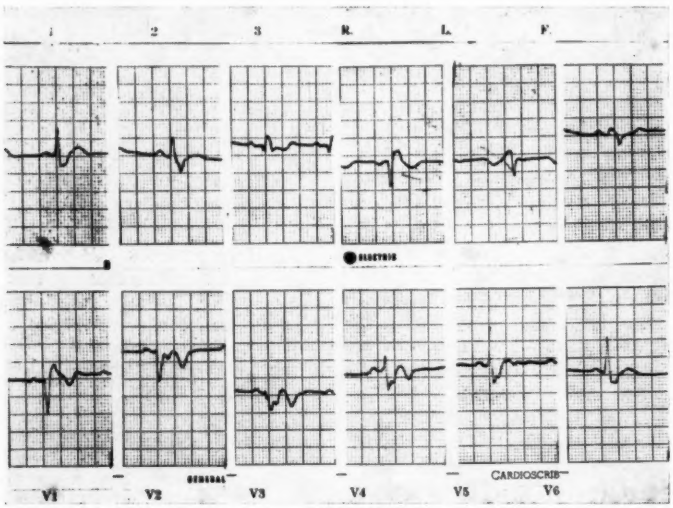

FIGURE I

February 20, 1954: Right bundle branch block

During further tapering off to 25 milligrammes every second day in March, 1955, grave attacks of ventricular tachycardia occurred, and a daily dosage of 75 milligrammes was resumed. The daily dosage was again reduced to 50 milligrammes in mid-July, 1955. Progressive reduction of dosage was again commenced in February, 1956, but the recurrence of further ventricular tachycardia indicated the resumption of the steroid administration at 50 milligrammes daily. A favourable effect of cortisone has been considered demonstrated by the clearing of apical shadows at a slow rate, but nevertheless a rate faster than would be expected in a natural remission (Figures II and III). Extensive tests in late 1955, after 18 months of cortisone therapy, showed no evidence of tuberculous infection. The Kveim test after James and Thomson (1955) gave a positive result on skin biopsy on November 25, 1955.

The occurrence and management of severe attacks of ventricular tachycardia have constituted the major problem in this case, and the details are of interest. The patient had a further "attack" of brief unconsciousness on June 5, 1954, and an "attack" with prolonged unconsciousness, deep cyanosis and stertor on July 3, 1954. The explanation of these attacks was not clear, but it was suspected (probably in error) that they were due to an intermittent complete heart block. His condition continued then to give little anxiety until the earlier tapering off of cortisone therapy was nearly complete in March, 1955. On March 20, 1955, he had a sudden "attack" with faintness, intractable vomiting, cyanosis, hypotension (? 80/? 65 mm. Hg), and electrocardiography showed ventricular tachycardia with a rate of 180 per minute. Urinary secretion ceased, and T.N.P.N. rose to 62 milligrammes per 100 cubic centimetre.

There was no response to rapid digitalization. Quinidine was avoided because of the fear that fatal Adams-Stokes phenomena might be induced. After 48 hours of ventricular tachycardia the rhythm reverted dramatically to normal, with the intravenous administration of 200 milligrammes of procaine amide ("Pronestyl", Squibb). This was followed by oral administration of 500 milligrammes four-hourly for three days. The oral administration of "Pronestyl", 500 milligrammes three times a day, was then tried as a regular suppressive measure. This induced some gastro-intestinal intolerance. Moreover, one felt that it did not suppress "attacks" and rendered the arrhythmia increasingly resistant to parenteral "Pronestyl" therapy in "attacks".

Attacks of ventricular tachycardia (rate *circum* 200 per minute) occurred on May 16, 1955 (with acute shortness of breath), on May 29, 1955 (like turning on a switch), on June 24, 1955 (unconscious on floor in drenching sweat), and on June 29, 1955 (like a switch again). The "Pronestyl" dosage was of necessity increased progressively, and routine dosage in "attacks" became 500 to 700 milligrammes given intravenously, combined with 300 to 500 milligrammes intramuscularly and three grains of sodium phenobarbitone intramuscularly for the usual persistent

vomiting. These doses were repeated when necessary within a few hours, and after the first attack were used promptly as domiciliary bedside treatment without hospital admission. Oral "Pronestyl" therapy was omitted from June, 1955, because of increasingly refractory arrythmia.

On June 30, 1955, regular digitaline (digitoxin) was commenced on trial as a suppressive drug, but after two weeks it became evident that a precarious basic

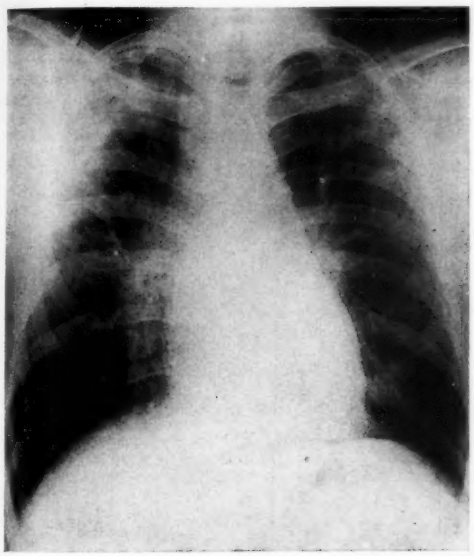

FIGURE II

August 31, 1953: Extensive abnormal opacities are seen in both lung fields with enlarged hilar shadows

rhythm was being induced. There were a few normal beats constantly interpolated with short bursts of five to nine beats of ventricular tachycardia. Digitaline therapy was stopped on July 14, 1955.

Quinidine sulphate was then given orally in spite of original misgivings and built up speedily to three grains four-hourly with good effect. Ventricular tachycardia broke through again on August 11, 1955, after a day of business strain. It was controlled by parenteral administration of "Pronestyl", and the quinidine dosage was then doubled. A further "attack" occurred on September 19, 1955; this was not controlled by prompt oral administration of quinidine, nine grains, but was controlled by intravenous injection of "Pronestyl", as was a similar "attack" on January 8, 1956, while the patient was on holiday. The "attacks" were considerably less frequent on quinidine suppression, and the patient's confidence now returned considerably. It appeared to be a safe drug in this case, and it was planned to use quinidine over a prolonged period in a dosage of at least six grains four times daily.

Further "attacks" of ventricular tachycardia occurred on March 13 and 20, 1956, and on April 10 and 19, 1956, following a similar pattern to those previously experienced. They occurred in mid-afternoon during quiet activity and responded to procaine amide.

In the first of these attacks he was unconscious for 75 minutes, in the second for five minutes. Electrocardiograms taken on March 20, 1956, when compared with the previous ones, showed a general loss of *T*-wave voltage with multiple ventricular ectopic beats. This had been accepted as indicating progressive ventricular defect, and it had been felt that an unfavourable outcome would not be long delayed. On April 22 and 28, 1956, he had Stokes-Adams attacks in bed at 10 p.m. and 11.30 p.m. These attacks were different in form from previous ones, and when he was examined promptly no rhythm change was evident. He died in a similar attack in bed on May 3, 1956, at 11.15 p.m. The mechanism appears to have been prolonged ventricular asystole.

Post-Mortem Findings

A post-mortem examination was made on May 4, 1956, and the findings were as follows.

The body was that of an obese rather plethoric male in early middle life. No glands were palpable in the axillæ, groins or neck. The thyroid gland was of normal size, two normal parathyroid glands were identified, and the cervical glands were apparently normal. The left lung weighed 19 ounces and the right lung 23 ounces. The pleural cavities were normal, apart from a few adhesions between the diaphragm and the adjacent lung. These were due to local,

FIGURE III

March 28, 1955: There is patchy infiltration in upper and middle zones of both lungs with some fibrosis. The hilar shadows are enlarged. There has been appreciable resolution since the film of August 31, 1953, and slight further improvement since the last film of November 2, 1954. The size of the heart shadow has increased since August 31, 1953

greyish, circumscribed, pleural inflammatory nodules, averaging 0·5 centimetre in diameter. The pleural aspects of both lungs showed numerous scattered tiny, round and frond-like, greyish lesions, slightly raised above the surface, some of which could be scraped off. There was puckering and scarring of both upper lobes without overlying adhesions. In section there was a

fibrous apical scar in the right upper lobe, with multiple small grey stellate scars throughout the parenchyma. In the middle lobe there were small white areas suggestive of bronchial abscesses. In the right lower lobe there were apical and subpleural scars, but the parenchyma was otherwise well aerated. The broncho-pulmonary nodes appeared yellow and fibrous in cut section. The left lung showed posterior and apical

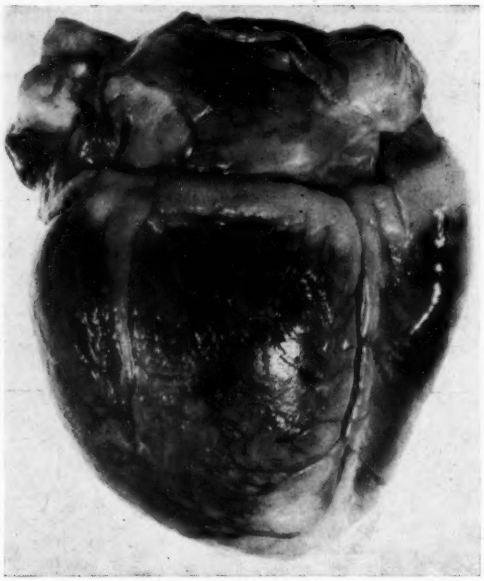

FIGURE IV

May 4, 1956: The heart *post mortem* showed numerous small yellow pericardial nodules of granular sarcoid material and weighed 19 ounces

scarring in the upper lobe, with numerous small fibrous areas. The lower lobe showed similar scars at the apex and in the posterior basal region with some brownish discoloration. There was gross enlargement of the right lateral tracheo-bronchial nodes, which measured up to five centimetres by three centimetres and extended downwards behind the main bronchus; also of the right paratracheal nodes. Those on the left side were considerably enlarged, but to a lesser extent. The inferior tracheo-bronchial nodes were not so much involved, and the para-aortic nodes appeared normal. The heart weighed 19 ounces (Figure IV). The external aspect showed small yellow pericardial granular nodules suggestive of the lesion seen in the lung. The aorta was normal, showing minimal atheroma.

There were no significant abnormalities in the abdomen or brain.

The parathyroids showed an unusual degree of fatty infiltration. In the lachrymal glands there was a slight diffuse chronic inflammatory infiltrate with two incompletely developed granulomata, and in the parotid very occasional small granulomata. In the inguinal and axillary nodes occasional sarcoid granulomata were seen with some hyalinized areas. The spleen showed congestion, scattered sarcoid granulomatous follicles and no evidence of older lesions. In the diaphragm could be seen both hyalinized confluent healed areas and active sarcoid tubercles in all stages, and in the liver was an occasional mid-zonal granuloma.

Examination of the heart revealed extensive scarring and hyalinization with numerous active granulomata extending from epicardial fat to endocardium (Figure V). Lesions in fat are sometimes in walls of veins. The left auricle was normal, and in the right ventricle granulomata in fat and hyalinized areas among muscle fibres were observed. The lungs showed extensive granulomata, some intra-alveolar and many in perivascular lymphatics, while others were in fibrous tissue. Large areas have progressed to hyalinization with some scanty calcification and cholesterol deposition. The pleural lesions are sarcoid granulomata. The hilar nodes showed hyalinization, with sarcoid granulomata.

The post-mortem examination confirmed the diagnosis of generalized sarcoidosis with extensive involvement of the heart.

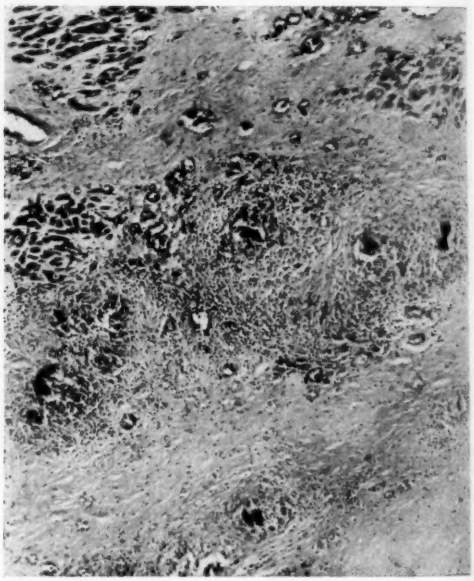

FIGURE V

Photomicrograph indicating heart lesions

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